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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

RE APPLICATION OF:

TETSUJI SUDOH ET AL

: GROUP ART UNIT: 1804

SERIAL NO: 08/192,800

FILED: FEBRUARY 7, 1994

: EXAMINER: LEGUYADER

FOR: PHYSIOLOGICALLY ACTIVE
POLYPEPTIDE AND DNA

#46
B.g.J.
12/14/95

APPEAL BRIEF

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

This is an appeal of the Examiner's Final Rejection, dated February 6, 1995, of Claims 2-7 and 10-35 in the above-identified application. A Notice of Appeal and the requisite fee were filed on July 13, 1995.

(1) Real Parties of Interest:

The real parties of interest include Daiichi Pure Chemical Co., Ltd., Daiichi Pharmaceutical Co., Ltd., and Hisayuki Matsuo.

(2) Related Appeals:

Appellants' undersigned representative is not aware of any related appeals.

(3) Status of Claims:

Claims 2-7 and 10-35 are pending and appealed in this application.

(4) Status of Amendments:

The claims have not been amended in response to the final rejection in the above-identified application.

(5) Summary of Invention:

The present invention concerns a cDNA consisting essentially of a base sequence encoding a polypeptide having one of the following amino acid sequences:

- (1) H-Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser
Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His-OH;
- (2) H-Gly Ser Gly Cys Phe Gly Arg Lys Met Asp Arg Ile
Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg
His-OH;
- (3) Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg
Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys
Lys Val Leu Arg Arg His;
- (4) His Pro Leu Gly Ser Pro Gly Ser Ala Ser Asp Leu Glu
Thr Ser Gly Leu Gln Glu Gln Arg Asn His Leu Gln Gly
Lys Leu Ser Glu Leu Gln Val Glu Gln Thr Ser Leu Glu
Pro Leu Gln Glu Ser Pro Arg Pro Thr Gly Val Trp Lys
Ser Arg Glu Val Ala Thr Glu Gly Ile Arg Gly His Arg
Lys Met Val Leu Tyr Thr Leu Arg Ala Pro Arg Ser Pro

Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met
Asp Arg Ile Ser Ser Ser Ser Gly Leu; and

- (5) Met Asp Pro Gln Thr Ala Pro Ser Arg Ala Leu Leu Leu
Leu Phe Leu His Leu Ala Phe Leu Gly Gly Arg Ser His
Pro Leu Gly Ser Pro Gly Ser Ala Ser Asp Leu Glu Thr
Ser Gly Leu Gln Glu Gln Arg Asn His Leu Gln Gly Lys
Leu Ser Glu Leu Gln Val Glu Gln Thr Ser Leu Glu Pro
Leu Gln Glu Ser Pro Arg Pro Thr Gly Val Trp Lys Ser
Arg Glu Val Ala Thr Glu Gly Ile Arg Gly His Arg Lys
Met Val Leu Tyr Thr Leu Arg Ala Pro Arg Ser Pro Lys
Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu
Arg Arg His.

The present invention also concerns a recombinant DNA
sequence comprising a base sequence encoding a polypeptide
having one of the amino acid sequences (1)-(5) above, as well
as a method of producing cDNA, comprising:

hybridizing a probe having a DNA sequence encoding a
part of porcine brain natriuretic peptide to a human cDNA
library;

selecting a positive clone; and

isolating said cDNA of said positive clone (see, for
example, page 3, lines 1-13, page 4, lines 15-19, page 5, last
two lines, page 6, lines 1-2 and 13-19, page 8, lines 1-16,
page 16, lines 2-10 and Fig. 2).

The present invention provides a means for obtaining a human brain natriuretic peptide (hBNP) which is expected to have considerably higher rectum relaxation activity, and thus, greater natriuretic and smooth muscle relaxation activities, than the corresponding hANP, based on the known 3- to 4-fold increase in the rectum relaxation activity of pBNP relative to pANP (see page 2, lines 3-15 and page 7, lines 3-7 from the bottom, of the present specification). Consequently, the present invention represents a significant and meaningful advancement in treatment of circulatory disease (page 2, lines 1-8 and 25-27).

Furthermore, as demonstrated by the factual evidence and statements in the executed Declaration of Dr. Tetsuji Sudoh dated October 12, 1994, and filed October 20, 1994, one of ordinary skill would not have had a reasonable expectation of success in arriving at the present invention from the knowledge in existence in the pertinent field at the time grandparent application Serial No. 07/486,827 was filed. Thus, the present invention is fully patentable.

(6) Issues:

1. Whether Claims 2-7 and 10-35 are obvious under 35 U.S.C. 103 over Maekawa et al in view of Maniatis, Sudoh et al (R), Sudoh et al (T), Oikawa et al and Vlasuk et al?

(7) Grouping of Claims:

The Claims do not stand or fall together.

Each claim is grouped individually. Accordingly, the claims are grouped as follows:

- Group I -- Claim 14;
- Group II -- Claim 15;
- Group III -- Claim 16;
- Group IV -- Claim 17;
- Group V -- Claim 18;
- Group VI -- Claim 19;
- Group VII -- Claim 20;
- Group VIII -- Claim 21;
- Group IX -- Claim 22;
- Group X -- Claim 23;
- Group XI -- Claim 24;
- Group XII -- Claim 25;
- Group XIII -- Claims 26 and 28;
- Group XIV -- Claim 27;
- Group XV -- Claim 29;
- Group XVI -- Claim 2;
- Group XVII -- Claim 3;
- Group XVIII -- Claim 4;
- Group XIX -- Claim 5;
- Group XX -- Claim 6;
- Group XXI -- Claim 7;
- Group XXII -- Claim 10;

Group XXIII -- Claim 11;
Group XXIV -- Claim 12;
Group XXV -- Claim 13;
Group XXVI -- Claim 30;
Group XXVII -- Claim 31 and 32;
Group XXVIII -- Claim 33;
Group XXIX -- Claim 34; and
Group XXX -- Claim 35.

(8) Argument:

(i) (ii)(iii): There are no rejections under 35 U.S.C. 112 or 35 U.S.C. 102 in this application.

(iv): The rejection of Claims under 35 U.S.C. 103 as being unpatentable over Maekawa et al in view of Maniatis, Sudoh et al (R), Sudoh et al (T), Oikawa et al and Vlasuk et al is in error, and should be withdrawn.

GROUP I -- CLAIM 14

As demonstrated by the factual evidence and statements in the executed Declaration of Dr. Tetsuji Sudoh dated October 12, 1994 and filed October 20, 1994, one of ordinary skill would not have had a reasonable expectation of success in arriving at the present invention from knowledge in existence at the time grandparent application Serial No. 07/486,827 was filed (March 1, 1990). Therefore, the present invention is fully patentable over the cited references.

The invention of Group I, Claim 14, concerns cDNA encoding human brain natriuretic peptide (hBNP). Maekawa et al disclose the cloning and sequence analysis of cDNA encoding a precursor for porcine brain natriuretic peptide (pBNP). Sudoh et al (R) disclose the sequences of porcine BNP. Sudoh et al (T) disclose a 32-amino acid-long brain natriuretic peptide identified in porcine brain. Oikawa et al disclose the structure of dog and rabbit precursors of atrial natriuretic peptides deduced from nucleotide sequences of cloned cDNA. Vlasuk et al disclose the structure and analysis of the bovine atrial natriuretic peptide precursor gene. Thus, the differences between the invention of Group I, Claim 14, and the disclosures of these references lie in the structures of the polynucleotides, the peptides encoded thereby, and the sources thereof.

On page 228, Maniatis et al teach a method for identifying cDNA clones corresponding to developmentally regulated mRNAs. A population of cDNA molecules enriched in sequences characteristic for a particular developmental stage is used to probe a cDNA or genomic library.

Given the equivalence of a cDNA and a genomic library taught by Maniatis et al on page 228, it is not clear how Maniatis et al cure the failure of Seilhamer et al (described below) to successfully isolate human DNA encoding a BNP using porcine cDNA. Maniatis et al suggest that the same result is obtainable using either a cDNA or a genomic library. Thus, if

one cannot achieve success with one library, Maniatis et al does not lead one to expect success using the other library.

Furthermore, the procedure of Maniatis et al appears to require use of a probe from the same tissue and the same species. For example, on page 227, Maniatis et al teach that differential hybridization (the technique relied upon by the Examiner) is used when mRNA preparations are available which contain many sequences in common, except for the presence or absence of a few species of interest. Differential hybridization is taught as being useful for identifying certain mRNAs which may be present in a particular sample in which production of the mRNA has been induced (e.g., by heat shock, drugs, hormones or a particular substrate). This strongly suggests that the genetic material for each of the mRNA preparations comes from the same source, but is treated differently in one of the preparations so as to induce the formation of a particular mRNA in that preparation.

Maniatis et al neither teach nor suggest that success can be achieved employing cDNA from one species to identify the inducible genes from a second species. Thus, the technique of differential hybridization appears to be relevant to obtaining a clone from the same species, based on the teachings of Maniatis et al immediately preceding the disclosure relied upon for the present rejection.

In the disclosure relied upon for the present rejection, Maniatis et al teach that cDNA prepared from mRNA obtained at

one developmental stage (stage 1) is hybridized to a 20-fold excess of mRNA obtained from another stage (stage 2), and the hybrid is removed. This procedure of Maniatis et al is then repeated twice more using a 50-100-fold excess of stage 2 mRNA. The unbound cDNA fraction is then hybridized to a 100-fold excess of stage 1 mRNA, and the hybrid is recovered. After removing the mRNA, the cDNA that is highly enriched in stage 1-specific sequences is used as a probe.

One would not reasonably expect success using the procedure described by Maniatis et al on page 228 if a probe from a different species is used. If mRNA from a different organism is used, the polynucleotide homology differences between the two organisms may be sufficiently great as to prevent hybridization, particularly since the two mRNA preparations are obtained from different developmental stages. A difference in the developmental stages induces differences in mRNAs, even when obtained from the same organism or cell. To minimize the differences between the two mRNAs and thus maximize the chances of success (note the prior teaching of Maniatis et al that the two mRNA preparations contain many sequences in common, but differ from each other based on the presence or absence of a few species of interest), it is apparent that Maniatis et al refer to mRNA obtained from different developmental stages of the same organism.

Based on the steps necessary to arrive at the present invention (hBNP) from the closest subject matter disclosed by

the cited references (pBNP), one must use a probe from a different species. The rejection cannot be properly based on use of a human DNA probe, because (1) the cited references do not disclose hBNP DNA and (2) use of any other human gene would lead to isolation and/or identification of that other human gene.

Furthermore, in the present invention, a cDNA library was prepared from mRNA obtained from a human tissue. The human BNP clone was screened using a cDNA fragment encoding porcine BNP-26 and the 30 bp upstream therefrom as a probe (page 14, lines 1-12 of the present specification). Fifty-five positive plaques were obtained (page 15, lines 2-3). Thus, it appears that the present polynucleotides were not obtained by differential hybridization. Accordingly, the relevance of the process of Maniatis et al, identified by the Examiner as being the process most pertinent to the present invention, is not understood.

Consequently, it is not seen how the teachings of Maniatis et al cure the deficiencies of the remaining cited references. The method of Maniatis et al appears to require that a probe from the same cell (i.e., the same tissue and the same species) be used. Further, there is no evidence that the method of Maniatis et al relied upon by the Examiner is reasonably likely to be successful in arriving at the present invention from the closest polynucleotides disclosed or

suggested by the cited references. Consequently, the present invention is fully patentable over the cited references.

However, assuming *arguendo* that it would have been obvious for one of ordinary skill in the art to use the porcine DNA sequence disclosed by Maekawa et al, or an effective portion thereof (as taught by Seilhamer et al [col. 8, lines 40-54]), as a probe to screen for the human BNP gene, the factual bases by which one of ordinary skill evaluates the expectation of success do not establish that one would have had a reasonable expectation of success in arriving at the present invention from the teachings of the cited references (see the Declaration of Sudoh dated October 12, 1994 and filed October 20, 1994). Thus, the evidence of record supports the patentability of the present invention.

For example, neither (1) the 70% degree of homology between human atrial natriuretic peptide (hANP) and porcine BNP (pBNP) taught by Sudoh et al (R) and (T) nor (2) the 50.6-65.7% degree of homology between hANP mRNA and pBNP mRNA taught by Maekawa et al is sufficiently high for one of ordinary skill to reasonably expect success in cloning and isolating the cDNA of one based on the sequence of the other (see paragraph 5, page 3 of the Declaration of Sudoh dated October 12, 1994 and filed October 20, 1994).

Further, Table 1 of Oikawa et al teaches that the homology between hANP and other mammalian ANPs is only 52-60%. Thus, assuming that one of ordinary skill expects the same

degree of homology between hBNP and other mammalian BNPs as is observed between hANP and other mammalian ANPs, Sudoh et al (R) and (T), Maekawa et al and Oikawa et al appear to indicate that the degree of homology is greater between pBNP and hANP than what one expects between pBNP and hBNP. As a result, one might expect a probe based on the pBNP gene to lead to cloning of a hANP gene, rather than a hBNP gene (see paragraph 6, pages 3-4 of the Declaration).

In addition, Sudoh et al (*Biochem. Biophys. Res. Comm.*, 159:1427-1434, submitted with and incorporated into the Declaration by reference) disclose that human and porcine ANP's have 89.7% and 100% identical residues in the pro-form and α -form, respectively (page 1433, lines 1-3). However, the high homology between the pro- and α -forms of hANP and pANP would lead one to reasonable expect success in cloning and isolating hBNP cDNA using a 10-20 bp pBNP probe, which the present Inventors attempted to do, but failed to successfully carry out (see paragraph 7, page 4 of the Declaration).

Thus, in addition to the failure of Seilhamer et al to isolate a polynucleic acid encoding hBNP using a porcine cDNA probe (discussed below), the present Inventors failed to obtain human BNP cDNA using a 10-20 bp pBNP probe. The failure of others to produce the claimed invention, and the arrival at a solution to unexpected and unforeseen problems have long been considered objective indicia of the non-obviousness of an invention. See Graham v. John Deere, 383

U.S. 1, 148 U.S.P.Q. 459 (1966); Eibel Process Co. v. Minnesota & Ontario Paper Co., 261 U.S. 45, 43 S.Ct. 322 (1923); and Reeves Instrument Corp. v. Beckman Instruments, Inc., 444 F.2d 263, 170 U.S.P.Q. 74 (9th Cir. 1971), cert. denied, 404 U.S. 751 (1971).

Furthermore, the low homology (70.0%) between human prepro-BNP and porcine prepro-BNP (results determined by the present Inventors, disclosed by Sudoh et al [*Biochem. Biophys. Res. Comm.*, 159:1427-1434]) presents a sharp contrast to the more highly conserved mammalian ANP's, thus introducing a further unexpected problem in cloning hBNP. This unexpected problem makes it surprising that hBNP cDNA could be cloned and isolated, given the level of ordinary skill and the knowledge in this field at the time of filing grandparent U.S. application Serial No. 07/486,827 (March 1, 1990) (see paragraph 9, page 4 of the Declaration of Sudoh).

Therefore, one of ordinary skill would not have had a reasonable expectation of success in arriving at the present invention from the knowledge present in the art at the time grandparent application Serial No. 07/486,827 was filed.

Furthermore, as discussed in the Amendment filed July 21, 1993 and the Preliminary Amendment filed February 7, 1994, Seilhamer et al, U.S. Patent No. 5,114,923, disclose that no conditions could be determined under which the cDNA encoding porcine BNP would hybridize to human DNA, even though there was every reason to believe that it would (see col. 8, lines

40-54 and col. 9, lines 32-35 and 45-47 of Seilhamer et al). However, Seilhamer et al successfully used the pBNP cDNA to retrieve genes encoding related proteins from other species, such as a pig, a rat, a dog, a cat and a rabbit (col. 9, lines 32-44).

Since Seilhamer et al successfully used the pBNP cDNA to retrieve the corresponding genes from five out of six species attempted, the assertion in the Official Action of February 6, 1995 (see page 4, lines 12-19) that it is not surprising that Seilhamer et al fail to isolate the human BNP genomic clone appears to be a hindsight reconstruction, rather than an accurate interpretation of the teachings of Seilhamer et al. Seilhamer et al specifically disclose:

"There was every reason to believe that porcine BNP should be capable of hybridizing to human NRP under appropriate conditions; however no conditions could be determined under which pBNP would hybridize to a human library. This was surprising in that, in an evolutionary sense, porcine BNP is more likely to be related to the corresponding human protein, than is a corresponding canine protein. It was thus unexpected that porcine BNP was unable to identify human NRP...." (col. 8, lines 44-54; emphasis added).

Consequently, the conclusion that it is not surprising that Seilhamer et al failed to isolate the human BNP genomic clone using pBNP cDNA is not accurate since Seilhamer et al themselves state that is surprising. As a result, the success of the present Inventors in obtaining DNA encoding human BNP is surprising and unexpected, particularly in view of the

page 412, Figure 1 of Maekawa et al). The formulas of porcine BNP-32 is compared to the formula of the cDNA of Group I, Claim 14, hereinbelow:

	1												13
pBNP-32:	Ser	Pro	Lys	Thr	Met	Arg	Asp	Ser	Gly	Cys	Phe	Gly	Arg
hBNP-23*:													
										Cys	Phe	Gly	Arg
	14												26
pBNP-32:	Arg	Leu	Asp	Arg	Ile	Gly	Ser	Leu	Ser	Gly	Leu	Gly	Cys
hBNP-23*:	Lys	Met	Asp	Arg	Ile	Ser	Ser	Ser	Ser	Gly	Leu	Gly	Cys
	27												32
pBNP-32:	Asn	Val	Leu	Arg	Arg	Tyr							
hBNP-23*:	Lys	Val	Leu	Arg	Arg	His							

*: formula (1) on p. 2 above

A number of differences exist in the amino acid sequence of pBNP-32 and the amino acid sequence encoded by the cDNA of Group I, Claim 14. A comparison of the codons which encode the different amino acid residues provides an indication of

the minimum number of differences in the corresponding polynucleic acids. A summary of the differences is presented in the following table, in which "N" refers to any nucleotide:

Position	Present Invention	Codons*	pBNP-32	Codons*
32	His	CAT CAC	Tyr	TAT TAC
27	Lys	AAA AAG	Asn	AAT AAC
21	Ser	AGT AGC TCN	Leu	TTA TTG CTC CTA CTG
19	Ser	AGT AGC TCN	Gly	GGN
15	Met	ATG	Leu	TTA TTG CTC CTA CTG
14	Lys	AAA AAG	Arg	AGA AGG CGN

*: The identities of the codons which encode each of the above amino acids was obtained from Dressler et al, "Discovering Enzymes," Scientific American Library Series, p. 186, (1991), submitted with the Amendment and Request for Reconsideration filed December 30, 1991.

As shown by the above table, for each difference in amino acid sequence, at least one difference in DNA sequence exists. Consequently, the structure of the cDNA of Group I, Claim 14, contains at least 6 differences from the structurally closest

polynucleotide possibly suggested by the cited references (pBNP).

The cited references do not suggest/ that the differences in structure between the cDNA of Group I, Claim 14, and the structurally closest possible polynucleotide of the cited references are desirable, or would even result in a cDNA which encodes a biologically active polypeptide. Consequently, one would not be motivated to make the structural changes to the structurally closest possible polynucleotide of the cited references necessary to arrive at the present cDNA and recombinant DNA sequence.

Even further, the cDNA of Group I, Claim 14, provides a means for obtaining a human natriuretic peptide (hBNP) which is expected to have considerably higher rectum relaxation activity and greater natriuretic and smooth muscle relaxation activities than the corresponding hANP, based on the known 3- to 4-fold increase in the rectum relaxation activity of pBNP relative to pANP (see page 2, lines 3-15 of the present specification). Consequently, the present cDNA represents a significant and meaningful advancement in the treatment of circulatory disease.

The evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the cDNA of Group I, Claim 14, based on the teachings and disclosures of the cited references. Further, the cDNA of Group I, Claim 14, is structurally non-obvious from the

closest possible polynucleotide suggested by the cited references. Therefore, the cDNA of Group I, Claim 14, is fully patentable over the cited references.

Furthermore, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the present DNA. Interestingly, as discussed above, both Seilhamer et al and Maniatis et al equate a genomic library with a cDNA library, thereby indicating that no unusual problems are expected in screening a genomic library. Even more interesting, the temperature conditions used by Seilhamer et al were less stringent (37-42°C; col. 9, lines 6-10 and 38-42) than those used by the present Inventors to obtain the present DNA (60°C; see page 14, line 19 of the present specification).

Therefore, the combined teachings of the cited references attest to the difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al. The cited references do not suggest that the modifications necessary to arrive at the present polynucleotides from the closest polynucleotide(s) disclosed in or suggested by the cited references are desirable, or would even result in a gene which encodes a functional polypeptide.

Therefore, Group I, Claim 14, is fully patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

In addition to the minimum of six structural differences between DNA encoding pBNP-32 (described by Maekawa et al and Sudoh et al) and the cDNA of Group I, Claim 14, the cDNA of Group II, Claim 15, shows at least one additional structural difference:

pBNP-32: 1
 Ser Pro Lys Thr Met Arg Asp Ser Gly Cys Phe Gly Arg 13
 hBNP-26*: Gly Ser Gly Cys Phe Gly Arg

¹⁴
pBNP-32: **Arg** **Leu** **Asp** **Arg** **Ile** **Gly** **Ser** **Leu** **Ser** **Gly** **Leu** **Gly** ²⁶
- - - - -
hBNP-26*: **Lys** **Met** **Asp** **Arg** **Ile** **Ser** **Ser** **Ser** **Ser** **Gly** **Leu** **Gly** **Cys**
- - - - -

pBNP-32: 27 32
Asn Val Leu Arg Arg Tyr
- - - -
hBNP-26*: Lys Val Leu Arg Arg His

*: see formula (2) on p. 2 above

By a similar analysis, the structure of the cDNA of Group II, Claim 15, contains at least 7 differences from the structurally closest possible polynucleotide of the cited references:

Position	Present Invention	Codons	pBNP-32	Codons
32	His	CAT CAC	Tyr	TAT TAC
27	Lys	AAA AAG	Asn	AAT AAC
21	Ser	AGT AGC TCN	Leu	TTA TTG CTC CTA CTG
19	Ser	AGT AGC TCN	Gly	GGN
15	Met	ATG	Leu	TTA TTG CTC CTA CTG
14	Lys	AAA AAG	Arg	AGA AGG CGN
7	Gly	GGN	Asp	GAT GAC

Thus, in addition to the differences in the codons encoding the amino acids at positions 14, 15, 19, 21, 27 and 32 of pBNP-32, the cDNA of Group II, Claim 15, contains a structurally different codon encoding the first amino acid of the sequence (corresponding to the position 7 of pBNP-32).

As described above for Group I, Claim 14, the evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the cDNA of Group II, Claim 15, based on the teachings and disclosures of the cited references. Further, the cDNA of Group II, Claim 15, is structurally non-obvious from the closest possible polynucleotide suggested by the cited references. Therefore, the cDNA of Group II, Claim 15, is fully patentable over the cited references.

Furthermore, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the present DNA. As discussed above, both Seilhamer et al and Maniatis et al indicate that no unusual problems are expected in screening a genomic library (in accordance with the procedures of Seilhamer et al). The combined teachings of the cited references thus attest to the unforeseen difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al.

The cited references do not suggest that the modifications necessary to arrive at the present polynucleotides from the closest polynucleotide(s) disclosed in or suggested by the cited references are desirable, or would even result in a gene which encodes a functional polypeptide. Thus, Group II, Claim 15, is fully and independently patentable over the cited references. As a

result, this ground of rejection is clearly and error, and should be withdrawn.

GROUP III -- CLAIM 16

Group III, Claim 16, depends from Group I, Claim 14. Therefore, Group III, Claim 16, includes all of the limitations of Group I, Claim 14, and all arguments presented above in support of Group I, Claim 14, are incorporated hereinbelow in support of Group III, Claim 16.

Group III, Claim 16, includes the further limitation that the cDNA further consists essentially of a base sequence encoding the amino acid sequence H-Ser-Pro-Lys-Met-Val-Gln-Gly-Ser-Gly covalently bound through a peptide bond to the N-terminal amino acid encoded by the cDNA of Claim 14.

In addition to the minimum of six structural differences between DNA encoding pBNP-32 (described by Maekawa et al and Sudoh et al) and the cDNA of Group I, Claim 14, the cDNA of Group III, Claim 16, shows at least four additional structural differences:

	1													13
pBNP-32:	Ser	Pro	Lys	Thr	Met	Arg	Asp	Ser	Gly	Cys	Phe	Gly	Arg	
hBNP-32 ¹ :	Ser	Pro	Lys	Met	Val	Gln	Gly	Ser	Gly	Cys	Phe	Gly	Arg	

	14													26
pBNP-32:	Arg	Leu	Asp	Arg	Ile	Gly	Ser	Leu	Ser	Gly	Leu	Gly	Cys	
hBNP-32 ¹ :	Lys	Met	Asp	Arg	Ile	Ser	Ser	Ser	Ser	Gly	Leu	Gly	Cys	

pBNP-32: ²⁷ **Asn** Val Leu Arg Arg ³² **Tyr**
 hBNP-32¹: **Lys** Val Leu Arg Arg **His**

¹: see formula (3) on p. 2 above

By a similar analysis to that shown above for Group I, Claim 14, the structure of the cDNA of Group III, Claim 16, contains at least 10 differences from the structurally closest possible polynucleotide of the cited references:

Position	Present Invention	Codons*	pBNP-32	Codons*
32	His	CAT CAC	Tyr	TAT TAC
27	Lys	AAA AAG	Asn	AAT AAC
21	Ser	AGT AGC TCN	Leu	TTA TTG CTC CTA CTG
19	Ser	AGT AGC TCN	Gly	GGN
15	Met	ATG	Leu	TTA TTG CTC CTA CTG
14	Lys	AAA AAG	Arg	AGA AGG CGN
7	Gly	GGN	Asp	GAT GAC

6	Gln	CAA CAG	Arg	AGA AGG CGN
5	Val	GTN	Met	ATG
4	Met	ATG	Thr	ACN

*: The identities of the codons which encode each of the above amino acids was obtained from Dressler et al, "Discovering Enzymes," Scientific American Library Series, p. 186, (1991), submitted with the Amendment and Request for Reconsideration filed December 30, 1991.

Thus, in addition to the differences in the codons encoding the amino acids at positions 14, 15, 19, 21, 27 and 32 of pBNP-32, the cDNA of Group III, Claim 16, contains four structurally different codons encoding the fourth through the seventh amino acids of the sequence (corresponding to positions 4-7 of pBNP-32).

As described above for Group I, Claim 14, the evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the cDNA of Group III, Claim 16, based on the teachings and disclosures of the cited references. Further, the cDNA of Group III, Claim 16, is structurally non-obvious from the closest possible polynucleotide suggested by the cited references, based on the minimum of 10 structural differences. Therefore, the cDNA of Group III, Claim 16, is fully and independently patentable over the cited references.

Furthermore, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the present DNA. As discussed above, both Seilhamer et al and Maniatis et al indicate that no unusual problems are expected in screening a genomic library (in accordance with the procedures of Seilhamer et al). The combined teachings of the cited references thus attest to the unforeseen difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al.

The cited references do not suggest that the modifications necessary to arrive at the cDNA of Group III, Claim 16, from the closest polynucleotide(s) disclosed in or suggested by the cited references are desirable, or would even result in a gene which encodes a functional polypeptide. Thus, Group III, Claim 16, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP IV -- CLAIM 17

Group IV, Claim 17, depends from Group III, Claim 16. Therefore, Group IV, Claim 17, includes all of the limitations of Groups I and III, Claims 14 and 16, and all arguments presented above in support of Groups I and III, Claims 14 and

16, are incorporated hereinbelow in support of Group IV, Claim 17.

Group IV, Claim 17, includes the further limitation that the cDNA further consists essentially of a base sequence encoding the following amino acid sequence covalently bound through a peptide bond to the N-terminal amino acid encoded by the cDNA of Claim 16:

His Pro Leu Gly Ser Pro Gly Ser Ala Ser Asp Leu Glu Thr Ser
Gly Leu Gln Glu Gln Arg Asn His Leu Gln Gly Lys Leu Ser Glu
Leu Gln Val Glu Gln Thr Ser Leu Glu Pro Leu Gln Glu Ser Pro
Arg Pro Thr Gly Val Trp Lys Ser Arg Glu Val Ala Thr Glu Gly
Ile Arg Gly His Arg Lys

In addition to the structural differences between DNA encoding pBNP-32 (described by Maekawa et al and Sudoh et al) and the cDNA of Group III, Claim 16, the cDNA of Group IV, Claim 17, encodes different amino acids at a large majority of the positions shown above.

The amino acid sequence recited above as the difference between Group IV, Claim 17, and Group III, Claim 16 (the "distinguishing" sequence), corresponds to the sequence disclosed by Maekawa et al in Figure 3 (page 414) from position 26 through position 99. Except for the first four and last four amino acids of each of these sequences, and the partial overlap between the two sequences at positions 52-64

of the pBNP polypeptide disclosed in Fig. 3 of Maekawa et al and positions 29-41 of the distinguishing sequence of Group IV, Claim 17, recited above, very little overlap exists.

Given the fact that there appears to be more differences than similarities in the codons of the cDNA of Group V, Claim 17, compared to the possible codons of the corresponding amino acid sequence recited in Figure 3 of Meakawa et al, Group IV, Claim 17, is fully and independently patentable over the cited references.

Furthermore, as described above for Groups I-III, Claims 14-16, the evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the cDNA of Group IV, Claim 17, based on the teachings and disclosures of the cited references. Further, the cDNA of Group IV, Claim 17, is structurally non-obvious from the closest possible polynucleotide suggested by the cited references, based on the greater number of structural differences than similarities in the codons of the distinguishing sequence. Therefore, the cDNA of Group IV, Claim 17, is fully and independently patentable over the cited references.

In addition, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the present DNA. As discussed above, both Seilhamer et al and Maniatis et al indicate that no unusual problems are expected in screening

a genomic library (in accordance with the procedures of Seilhamer et al). The combined teachings of the cited references thus attest to the unforeseen difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al.

The cited references do not suggest that the modifications necessary to arrive at the cDNA of Group IV, Claim 17, from the closest polynucleotide(s) disclosed in or suggested by the cited references are desirable, or would even result in a gene which encodes a functional polypeptide. Thus, Group IV, Claim 17, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP V -- CLAIM 18

Group V, Claim 18, depends from Group IV, Claim 17. Therefore, Group V, Claim 18, includes all of the limitations of Groups I, III and IV, Claims 14, 16 and 17, and all arguments presented above in support of Groups I, III and IV, Claims 14, 16 and 17, are incorporated hereinbelow in support of Group V, Claim 18.

Group V, Claim 18, includes the further limitation that the cDNA further consists essentially of a base sequence encoding the following amino acid sequence covalently bound

through a peptide bond to the N-terminal amino acid encoded by the cDNA of Claim 17:

Met Asp Pro Gln Thr Ala Pro Ser Arg Ala Leu Leu Leu Leu
Leu Phe Leu His Leu Ala Phe Leu Gly Gly Arg Ser

In addition to the vast structural differences between DNA encoding pBNP-32 (described by Maekawa et al and Sudoh et al) and the cDNA of Group IV, Claim 17, the cDNA of Group V, Claim 18, shows at least eleven additional structural differences.

The distinguishing sequence recited in Claim 18 corresponds to the first 26 amino acids recited in the sequence of Figure 3 of Maekawa et al. These sequences differ at positions 2, 4, 5, 7, 8, 10, 15, 16, 20, 21 and 24. Thus, there are at least 11 different codons in the comparison between the distinguishing base sequence of Group V, Claim 18, and the sequence suggested by Figure 3 of Maekawa et al. Consequently, at least 11 additional structural differences exist between the cDNA of Group V, Claim 18, and the possible sequences which encode the amino acid sequence recited in Figure 3 of Maekawa et al, the closest sequence disclosed by the cited references.

Accordingly, Group V, Claim 18, is fully and independently patentable over the cited references.

Furthermore, as described above for Groups I-IV, Claims 14-17, the evidence of record clearly establishes that no

reasonable expectation of success existed in arriving at the cDNA of Group V, Claim 18, based on the teachings and disclosures of the cited references. Further, the cDNA of Group V, Claim 18, is structurally non-obvious from the closest possible polynucleotide suggested by the cited references, based on the vast number of structural differences. Therefore, the cDNA of Group V, Claim 18, is fully and independently patentable over the cited references.

In addition, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the present DNA. As discussed above, both Seilhamer et al and Maniatis et al indicate that no unusual problems are expected in screening a genomic library (in accordance with the procedures of Seilhamer et al). The combined teachings of the cited references thus attest to the unforeseen difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al.

The cited references do not suggest that the modifications necessary to arrive at the cDNA of Group V, Claim 18, from the closest polynucleotide(s) disclosed in or suggested by the cited references are desirable, or would even result in a gene which encodes a functional polypeptide. Thus, Group V, Claim 18, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP VI -- CLAIM 19

Group VI, Claim 19, depends from Group I, Claim 14. Therefore, Group VI, Claim 19, includes all of the limitations of Group I, Claim 14, and all arguments presented above in support of Group I, Claim 14, are incorporated hereinbelow in support of Group VI, Claim 19.

Group VI, Claim 19, includes the further limitation that the cDNA has the following base sequence:

TGC TTT GGG AGG AAG ATG GAC CGG ATC AGC TCC TCC
AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT

Comparing the base sequence recited in Claim 19 with the base sequence recited from base number 325 through base number 393 in Figure 3 of Maekawa et al, at least 12 differences are observed (in particular, at positions 10, 14, 16, 28, 34, 35, 39, 54, 60, 64, 67 and 69). Thus, given the structural differences between the base sequence recited in Group VI, Claim 19, and the closest base sequence recited in the cited references, Group VI, Claim 19 is fully and independently patentable over the cited references.

Furthermore, as described above for Group I, Claim 14, the evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the cDNA of Group VI, Claim 19, based on the teachings and disclosures of the cited references. Further, the cDNA of Group VI, Claim 19, is structurally non-obvious from the closest possible

polynucleotide suggested by the cited references, based on the minimum of 12 structural differences. Therefore, the cDNA of Group VI, Claim 19, is fully and independently patentable over the cited references.

In addition, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the present DNA. As discussed above, both Seilhamer et al and Maniatis et al indicate that no unusual problems are expected in screening a genomic library (in accordance with the procedures of Seilhamer et al). The combined teachings of the cited references thus attest to the unforeseen difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al.

The cited references do not suggest that the modifications necessary to arrive at the cDNA of Group VI, Claim 19, from the closest polynucleotide(s) disclosed in or suggested by the cited references are desirable, or would even result in a gene which encodes a functional polypeptide. Thus, Group VI, Claim 19, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP VII -- CLAIM 20

Group VII, Claim 20, depends from Group II, Claim 15. Therefore, Group VII, Claim 20, includes all of the limitations of Groups I and II, Claims 14 and 15, and all arguments presented above in support of Groups I and II, Claims 14 and 15, are incorporated hereinbelow in support of Group VII, Claim 20.

Group VII, Claim 20, includes the further limitation that the cDNA has the following base sequence:

GGG TCT GGC TGC TTT GGG AGG AAG ATG GAC CGG ATC AGC
TCC TCC AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT

In addition to the differences in the sequences as described above for Group VI, Claim 19, the cDNA of Group VII, Claim 20, contains two additional structural differences in the first codon (GGG), whereas the corresponding sequence of Maekawa et al is GAC. Thus, Group VII, Claim 20 is fully and independently patentable over the cited references.

Furthermore, as described above for Group I, Claim 14, the evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the cDNA of Group VII, Claim 20, based on the teachings and disclosures of the cited references. Further, the cDNA of Group VII, Claim 20, is structurally non-obvious from the closest possible polynucleotide suggested by the cited references, based on the minimum of 14 structural differences. Therefore, the cDNA of

Group VII, Claim 20, is fully and independently patentable over the cited references.

In addition, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the present DNA. As discussed above, both Seilhamer et al and Maniatis et al indicate that no unusual problems are expected in screening a genomic library (in accordance with the procedures of Seilhamer et al). The combined teachings of the cited references thus attest to the unforeseen difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al.

The cited references do not suggest that the modifications necessary to arrive at the cDNA of Group VII, Claim 20, from the closest polynucleotide(s) disclosed in or suggested by the cited references are desirable, or would even result in a gene which encodes a functional polypeptide. Thus, Group VII, Claim 20, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP VIII -- CLAIM 21

Group VIII, Claim 21, depends from Group III, Claim 16. Therefore, Group VIII, Claim 21, includes all of the limitations of Groups I and III, Claims 14 and 16, and all

arguments presented above in support of Groups I and III, Claims 14 and 16, are incorporated hereinbelow in support of Group VIII, Claim 21.

Group VIII, Claim 21, includes the further limitation that the cDNA has the following base sequence:

AGC CCC AAG ATG GTG CAA GGG TCT GGC TGC TTT
GGG AGG AAG ATG GAC CGG ATC AGC TCC TCC AGT
GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT

In addition to the differences described above between the cDNA of Groups III and VII, Claims 16 and 20, and the DNA of Maekawa et al, the distinguishing base sequence recited in Group VIII, Claim 21, contains four additional structural differences in the 4th, 5th and 6th codons (compare with position 307-315 of Figure 3 of Maekawa et al). Accordingly, in view of the minimum of 18 structural differences between the cDNA of Group VIII, Claim 21, and the structurally closest sequence disclosed by the cited references, Group VIII, Claim 21, is fully and independently patentable over the cited references.

In addition, as described above for Groups I and III, Claims 14 and 16, the evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the cDNA of Group VIII, Claim 21, based on the teachings and disclosures of the cited references. Further, the cDNA of Group VIII, Claim 21, is structurally non-obvious from the

closest possible polynucleotide suggested by the cited references, based on the minimum of 18 structural differences. Therefore, the cDNA of Group VIII, Claim 21, is fully and independently patentable over the cited references.

Furthermore, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the present DNA. As discussed above, both Seilhamer et al and Maniatis et al indicate that no unusual problems are expected in screening a genomic library (in accordance with the procedures of Seilhamer et al). The combined teachings of the cited references thus attest to the unforeseen difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al.

The cited references do not suggest that the modifications necessary to arrive at the cDNA of Group VIII, Claim 21, from the closest polynucleotide(s) disclosed in or suggested by the cited references are desirable, or would even result in a gene which encodes a functional polypeptide. Thus, Group VIII, Claim 21, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP IX -- CLAIM 22

Group IX, Claim 22, depends from Group IV, Claim 17. Therefore, Group IX, Claim 22, includes all of the limitations of Groups I, III and IV, Claims 14, 16 and 17, and all arguments presented above in support of Groups I, III and IV, Claims 14, 16 and 17, are incorporated hereinbelow in support of Group IX, Claim 22.

Group IX, Claim 22, includes the further limitation that the cDNA has the following base sequence:

CAC CCG CTG GGC AGC CCC GGT TCA GCC TCG GAC TTG GAA ACG TCC
GGG TTA CAG GAG CAG CGC AAC CAT TTG CAG GGC AAA CTG TCG GAG
CTG CAG GTG GAG CAG ACA TCC CTG GAG CCC CTC CAG GAG AGC CCC
CGT CCC ACA GGT GTC TGG AAG TCC CGG GAG GTA GCC ACC GAG GGC
ATC CGT GGG CAC CGC AAA ATG CTC CTC TAC ACC CTG CGG GCA CCA
CGA AGC CCC AAG ATG GTG CAA GGG TCT GGC TGC TTT GGG AGG AAG
ATG GAC CGG ATC AGC TCC TCC AGT GGC CTG GGC TGC AAA GTG CTG
AGG CGG CAT

A cursory comparison of the distinguishing sequence of Group IX, Claim 22, with the sequence disclosed by Maekawa et al in Figure 3 from position 67 through position 298 reveals structural differences in nearly every codon. One of ordinary skill would have little expectation that the nucleotide disclosed by Maekawa et al would be likely to suggest or lead to the cDNA of Group IX, Claim 22. Thus, Group IX, Claim 22,

is fully and independently patentable over the cited references.

Furthermore, as described above for Groups I, III and IV, Claims 14, 16 and 17, the evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the cDNA of Group IX, Claim 22, based on the teachings and disclosures of the cited references. Further, the cDNA of Group IX, Claim 22, is structurally non-obvious from the closest possible polynucleotide suggested by the cited references, based on the vast structural differences therebetween. Therefore, the cDNA of Group IX, Claim 22, is fully and independently patentable over the cited references.

In addition, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the present DNA. As discussed above, both Seilhamer et al and Maniatis et al indicate that no unusual problems are expected in screening a genomic library (in accordance with the procedures of Seilhamer et al). The combined teachings of the cited references thus attest to the unforeseen difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al.

The cited references do not suggest that the modifications necessary to arrive at the cDNA of Group IX, Claim 22, from the closest polynucleotide(s) disclosed in or suggested by the cited references are desirable, or would even

result in a gene which encodes a functional polypeptide. Thus, Group IX, Claim 22, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP X -- CLAIM 23

Group X, Claim 23, depends from Group V, Claim 18. Therefore, Group X, Claim 23, includes all of the limitations of Groups I, III, IV and V, Claims 14, 16, 17 and 18, and all arguments presented above in support of Groups I, III, IV and V, Claims 14, 16, 17 and 18, are incorporated hereinbelow in support of Group X, Claim 23.

Group X, Claim 23, includes the further limitation that the cDNA has the following base sequence:

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ATG GAT CCC CAG ACA GCA CCT TCC CGG GCG CTC CTG CTC CTG CTC
TTC TTG CAT CTG GCT TTC CTG GGA GGT CGT TCC CAC CCG CTG GGC
AGC CCC GGT TCA GCC TCG GAC TTG GAA ACG TCC GGG TTA CAG GAG
CAG CGC AAC CAT TTG CAG GGC AAA CTG TCG GAG CTG CAG GTG GAG
CAG ACA TCC CTG GAG CCC CTC CAG GAG AGC CCC CGT CCC ACA GGT
GTC TGG AAG TCC CGG GAG GTA GCC ACC GAG GGC ATC CGT GGG CAC
CGC AAA ATG GTC CTC TAC ACC CTG CGG GCA CCA CGA AGC CCC AAG
ATG GTG CAA GGG TCT GGC TGC TTT GGG AGG AAG ATG GAC CGG ATC
AGC TCC TCC AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT
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In addition to the differences described above between the cDNA of Groups V and IX, Claims 18 and 22, and the DNA of Maekawa et al, the distinguishing base sequence recited in Group X, Claim 23, contains numerous additional structural differences in the 4th, 5th and 6th codons (compare, for example, the first 66 bases of the sequence of Group X, Claim 23, with positions 1-66 of Figure 3 of Maekawa et al). Accordingly, in view of the structural differences between the cDNA of Group X, Claim 23, and the structurally closest sequence disclosed by the cited references, Group X, Claim 23, is fully and independently patentable over the cited references.

In addition, as described above for Groups I, III, IV and V, Claims 14, 16, 17 and 18, the evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the cDNA of Group X, Claim 23, based on the teachings and disclosures of the cited references. Further, the cDNA of Group X, Claim 23, is structurally non-obvious from the closest possible polynucleotide suggested by the cited references, based on the structural differences therebetween. Therefore, the cDNA of Group X, Claim 23, is fully and independently patentable over the cited references.

Furthermore, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the present DNA. As discussed above, both Seilhamer et al and Maniatis et

al indicate that no unusual problems are expected in screening a genomic library (in accordance with the procedures of Seilhamer et al). The combined teachings of the cited references thus attest to the unforeseen difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al.

The cited references do not suggest that the modifications necessary to arrive at the cDNA of Group X, Claim 23, from the closest polynucleotide(s) disclosed in or suggested by the cited references are desirable, or would even result in a gene which encodes a functional polypeptide. Thus, Group X, Claim 23, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XI -- CLAIM 24

Group XI, Claim 24, depends from Group I, Claim 14. Therefore, Group XI, Claim 24, includes all of the limitations of Group I, Claim 14, and all arguments presented above in support of Group I, Claim 14, are incorporated hereinbelow in support of Group IX, Claim 24.

Group XI, Claim 24, includes the further limitation that the cDNA is obtained by screening a human cDNA library. Both Seilhamer et al and Maniatis et al indicate that no unusual problems are expected in screening a genomic library. The references suggest that one will obtain similar results when

screening either a genomic library or a cDNA library (particularly see Maniatis). However, as discussed above, Seilhamer et al were unable to obtain cDNA encoding hBNP when screening a genomic library.

In contrast to the unexpected inability of Seilhamer et al to obtain cDNA encoding hBNP, the present Inventors were able to obtain cDNA encoding hBNP when screening a cDNA library. Thus, Group XI, Claim 24 is directed precisely to the manner in which the problems encountered by Seilhamer et al can be overcome. Consequently, Group XI, Claim 24 is fully and independently patentable over the cited references.

Furthermore, the evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the cDNA of Group XI, Claim 24, obtained by screening a cDNA library, based on the teachings and disclosures of the cited references discussed in detail above. The clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors and recited in Group XI, Claim 24, also attests to the nonobviousness of the cDNA of Group XI, Claim 24.

The combined teachings of the cited references thus attest to the unforeseen difficulties encountered in arriving at the cDNA of Group XI, Claim 24, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al. The cited references do not suggest that the means to arrive at the cDNA of Group XI, Claim 24, from the closest polynucleotide(s)

disclosed in or suggested by the cited references would result in successfully obtaining a gene which encodes a functional brain natriuretic polypeptide. Thus, Group XI, Claim 24, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XII -- CLAIM 25

Group XII, Claim 25, depends from Group XI, Claim 24. Therefore, Group XII, Claim 25, includes all of the limitations of Groups I and XI, Claims 14 and 24, and all arguments presented above in support of Groups I and XI, Claims 14 and 24, are incorporated hereinbelow in support of Group XII, Claim 25.

Group XII, Claim 25, includes the further limitation that the human cDNA library is screened by hybridizing a probe having a DNA sequence encoding a part of porcine brain natriuretic peptide. In addition to the lack of problems taught by Seilhamer et al and Maniatis et al to expect in screening a genomic library, Seilhamer et al were unable to obtain cDNA encoding hBNP when using a cDNA probe encoding a part of pBNP, regardless of the conditions used.

By contrast, the present Inventors were able to use a cDNA probe encoding a part of porcine BNP to isolate human BNP, thus succeeding where Seilhamer et al failed. Furthermore, since it was reasonable to believe at the time of

the invention that one could not obtain the cDNA of Group XII, Claim 25, using the means recited in Group XII, Claim 25, the cDNA of Group XIII, Claim 25, is fully and independently patentable over the cited references.

As discussed above in support of Group XI, Claim 24, the evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the cDNA of Group XII, Claim 25, by hybridizing a probe having a DNA sequence encoding a part of porcine brain natriuretic peptide to a human DNA library, based on the teachings and disclosures of the cited references discussed in detail above. The clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors and recited in Group XII, Claim 25, also attests to the nonobviousness of the cDNA of Group XII, Claim 25.

The combined teachings of the cited references thus attest to the unforeseen difficulties encountered in arriving at the cDNA of Group XII, Claim 25, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al. The cited references do not suggest that the means to arrive at the cDNA of Group XII, Claim 25, from the closest polynucleotide(s) disclosed in or suggested by the cited references would result in successfully obtaining a gene which encodes a functional brain natriuretic polypeptide. Thus, Group XII, Claim 25, is fully and independently patentable over the cited references.

As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XIII -- CLAIMS 26 and 28

Group XIII, Claims 26 and 28, depends from Group XII, Claim 25. Therefore, Group XIII, Claims 26 and 28, includes all of the limitations of Groups I, XI and XII, Claims 14, 24 and 25, and all arguments presented above in support of Groups I, XI and XII, Claims 14, 24 and 25, are incorporated hereinbelow in support of Group XIII, Claims 26 and 28.

Group XIII, Claims 26 and 28, include the further limitation that the pBNP cDNA probe is obtained by digesting a complete or incomplete cDNA clone encoding porcine brain natriuretic peptide with endonucleases XhoI and RsaI. Although Oikawa et al suggest cleaving dog and rabbit cDNA encoding atrial natriuretic polypeptides with RsaI, the cited references are silent with regard to preparing a probe by either (1) digesting any DNA encoding a porcine natriuretic peptide or a brain natriuretic peptide, or (2) digesting any DNA with XhoI. Consequently, the cited references cannot suggest obtaining a probe by digesting a complete or incomplete cDNA clone encoding porcine brain natriuretic peptide with endonucleases XhoI and RsaI.

As a result, the cDNA of Group XIII, Claims 26 and 28, is fully and independently patentable over the cited references.

Therefore, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XIV -- CLAIM 27

Group XIV, Claim 27, depends from Group XIII, Claim 26. Therefore, Group XIV, Claim 27, includes all of the limitations of Groups I, XI, XII and XIII, Claims 14, 24, 25 and 26, and all arguments presented above in support of Groups I, XI, XII and XIII, Claims 14, 24, 25 and 26, are incorporated hereinbelow in support of Group XIV, Claim 27.

Group XIV, Claim 27, includes the further limitation that the pBNP cDNA probe encodes the amino acid sequence H-Gly Ser Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His-OH, the sequence recited in Group II, Claim 15. Thus, the arguments presented above in support of Group II, Claim 15, are also incorporated hereinbelow in support of Group XIV, Claim 27.

As discussed above in support of the cDNA of Group II, Claim 15, at least 7 structural differences exist between the cDNA of Group XIV, Claim 27, the structurally most similar DNA sequence of the cited references, based on the differences in the corresponding amino acid sequences. Furthermore, the cited references are silent with regard to preparing a probe by either (1) digesting any DNA encoding a porcine natriuretic peptide or a brain natriuretic peptide, or (2) digesting any

DNA with XhoI. Consequently, the cited references cannot and do not suggest the cDNA of Group XIV, Claim 27.

As a result, the cDNA of Group XIV, Claim 27, is fully and independently patentable over the cited references. Therefore, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XV -- CLAIM 29

Group XV, Claim 29, depends from Group XIV, Claim 27. Therefore, Group XV, Claim 29, includes all of the limitations of Groups I, XI, XII, XIII and XIV, Claims 14, 24, 25, 26 and 27, and all arguments presented above in support of Groups I, XI, XII, XIII and XIV, Claims 14, 24, 25, 26 and 27, are incorporated hereinbelow in support of Group XV, Claim 29.

Group XV, Claim 29, includes the further limitation that the pBNP cDNA probe consists essentially of the following base sequence CGG GCA CCA CGA AGC CCC AAG ATG GTG CAA GGG TCT GGC TGC TTT GGG AGG AAG ATG GAC CGG ATC AGC TCC TCC AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT, a sequence combining that recited in Group VIII, Claim 21, and the preceding four codons as recited in Group IX, Claim 22. Thus, the arguments presented above in support of Group VIII, Claim 21, are also incorporated hereinbelow in support of Group XV, Claim 29.

As discussed above in support of the cDNA of Group VIII, Claim 21, at least 18 structural differences exist between the cDNA of Group VIII, Claim 21, and the structurally closest

sequence disclosed by the cited references, based on the differences in the corresponding DNA sequences. Furthermore, four additional structural differences exist in the preceding four codons. Thus, at least 22 structural differences exist between the cDNA of Group XV, Claim 29, and the structurally closest sequence disclosed by the cited references (Maekawa et al, Fig. 3, from position 286 to position 393).

Additionally, as discussed above in support of Groups XIII and XIV, Claims 26-28, the cited references are silent with regard to preparing a probe by either (1) digesting any DNA encoding a porcine natriuretic peptide or a brain natriuretic peptide, or (2) digesting any DNA with XhoI. Consequently, the cited references cannot and do not suggest the cDNA of Group XV, Claim 29.

As a result, the cDNA of Group XV, Claim 29, is fully and independently patentable over the cited references. Therefore, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XVI -- CLAIM 10

Group XVI, Claim 10, concerns a recombinant DNA sequence comprising a base sequence encoding a polypeptide having the amino acid sequence H-Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His-OH, the sequence recited in Group I, Claim 14. Therefore, the

arguments presented above in support of Group I, Claim 14, are incorporated hereinbelow in support of Group XVI, Claim 10.

As discussed in support of Group I, Claim 14, for each difference in the amino acid sequence encoded by the recombinant DNA sequence of Group XVI, Claim 10, and the structurally closest DNA sequence of the cited references (shown in Fig. 3 of Maekawa et al), at least one difference in DNA sequence exists. Consequently, the structure of the recombinant DNA sequence of Group XVI, Claim 10, contains at least 6 differences from the structurally closest polynucleotide suggested by the cited references.

The cited references do not suggest that the differences in structure between the recombinant DNA sequence of Group XVI, Claim 10, and the structurally closest polynucleotide of the cited references are desirable, or would even result in a which recombinant DNA sequence encodes a biologically active polypeptide. Consequently, one would not be motivated to make the structural changes to the structurally closest possible polynucleotide of the cited references necessary to arrive at the present recombinant DNA sequence.

Even further, the recombinant DNA sequence of Group XVI, Claim 10, provides a means for obtaining a human natriuretic peptide (hBNP) which is expected to have considerably higher rectum relaxation activity and greater natriuretic and smooth muscle relaxation activities than the corresponding hANP, based on the known 3- to 4-fold increase in the rectum

relaxation activity of pBNP relative to pANP (see page 2, lines 3-15 of the present specification). Consequently, the present recombinant DNA sequence represents a significant and meaningful advancement in the treatment of circulatory disease.

The evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the recombinant DNA sequence of Group XVI, Claim 10, based on the teachings and disclosures of the cited references. Further, the recombinant DNA sequence of Group XVI, Claim 10, is structurally non-obvious from the closest possible polynucleotide suggested by the cited references. Therefore, the recombinant DNA sequence of Group XVI, Claim 10, is fully patentable over the cited references.

Furthermore, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the present recombinant DNA sequence. Interestingly, as discussed above, both Seilhamer et al and Maniatis et al equate a genomic library with a cDNA library, thereby indicating that no unusual problems are expected in screening a genomic library. Even more interesting, the temperature conditions used by Seilhamer et al were less stringent (37-42°C; col. 9, lines 6-10 and 38-42) than those used by the present Inventors to obtain the present DNA sequence (60°C; see page 14, line 19 of the present specification).

Therefore, the combined teachings of the cited references attest to the difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al. The cited references do not suggest that the modifications necessary to arrive at the present polynucleotides from the closest polynucleotide(s) disclosed in or suggested by the cited references are desirable, or would even result in a gene which encodes a functional polypeptide.

Consequently, Group XVI, Claim 10, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XVII -- CLAIM 11

Group XVII, Claim 11, depends from Group XVI, Claim 10. Therefore, Group XVII, Claim 11, includes all of the limitations of Group XVI, Claim 10, and all arguments presented above in support of Group XVI, Claim 10, are incorporated hereinbelow in support of Group XVII, Claim 11.

Group XVII, Claim 11, includes the further limitation that the polypeptide encoded by the recombinant DNA sequence further comprises the amino acid sequence H-Gly-Ser-Gly covalently bound to the H-Cys amino acid through a peptide bond. Thus, the recombinant DNA sequence of Group XVII, Claim 11, encodes a polypeptide sharing a common sequence with the

polypeptide encoded by the cDNA of Group II, Claim 15. Therefore, the arguments presented above in support of Group II, Claim 15, are also incorporated hereinbelow in support of Group XVII, Claim 11.

As discussed in support of Group II, Claim 15, in addition to the differences in the codons encoding the amino acids at positions 14, 15, 19, 21, 27 and 32 of pBNP-32, the recombinant DNA sequence of Group XVII, Claim 11, contains a structurally different codon encoding the first amino acid of the sequence (corresponding to the position 7 of pBNP-32). Thus, the recombinant DNA sequence of Group XVII, Claim 11, is structurally non-obvious from the closest possible polynucleotide suggested by the cited references in view of the minimum of seven structural differences therebetween. Consequently, the recombinant DNA sequence of Group XVII, Claim 11, is fully and independently patentable over the cited references.

Furthermore, the evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the recombinant DNA sequence of Group XVII, Claim 11, based on the teachings and disclosures of the cited references. In addition, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the recombinant DNA sequence of Group XVII, Claim 11. As discussed above, both Seilhamer et al and Maniatis et al indicate that no unusual problems are

expected in screening a genomic library (in accordance with the procedures of Seilhamer et al). The combined teachings of the cited references thus attest to the unforeseen difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al.

The cited references do not suggest that the modifications necessary to arrive at the present polynucleotides from the closest polynucleotide(s) disclosed in or suggested by the cited references are desirable, or would even result in a gene which encodes a functional polypeptide. Thus, Group XVII, Claim 11, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XVIII -- CLAIM 12

Group XVIII, Claim 12, depends from Group XVI, Claim 10. Therefore, Group XVIII, Claim 12, includes all of the limitations of Group XVI, Claim 10, and all arguments presented above in support of Group XVI, Claim 10, are incorporated hereinbelow in support of Group XVIII, Claim 12.

Group XVIII, Claim 12, includes the further limitation that the recombinant DNA sequence has the base sequence TGC TTT GGG AGG AAG ATG GAC CGG ATC AGC TCC TCC AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT, the sequence of Group VI, Claim 19. Therefore, the arguments presented above in support of Group VI, Claim 19, are also incorporated hereinbelow in support of Group XVIII, Claim 12.

As discussed in support of Group VI, Claim 19, a comparison of the sequence of Groups VI and XVIII, Claims 19 and 12, with the base sequence recited from base number 325 through base number 393 in Figure 3 of Maekawa et al shows at least 12 structural differences (in particular, at positions 10, 14, 16, 28, 34, 35, 39, 54, 60, 64, 67 and 69). Thus, given the structural differences between the base sequence recited in Group XVIII, Claim 12, and the closest base sequence recited in the cited references, Group XVIII, Claim 12, is fully and independently patentable over the cited references.

Furthermore, the evidence of record clearly establishes that no reasonable expectation of success existed in arriving

at the recombinant DNA sequence of Group XVIII, Claim 12, based on the teachings and disclosures of the cited references. In addition, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the recombinant DNA sequence of Group XVIII, Claim 12. As discussed above, both Seilhamer et al and Maniatis et al indicate that no unusual problems are expected in screening a genomic library (in accordance with the procedures of Seilhamer et al). The combined teachings of the cited references thus attest to the unforeseen difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al.

The cited references do not suggest that the modifications necessary to arrive at the present polynucleotides from the closest polynucleotide(s) disclosed in or suggested by the cited references are desirable, or would even result in a gene which encodes a functional polypeptide. Thus, Group XVIII, Claim 12, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XIX -- CLAIM 13

Group XIX, Claim 13, depends from Group XVI, Claim 11. Therefore, Group XIX, Claim 13, includes all of the limitations of Groups XVI and XVII, Claims 10 and 11, and all arguments presented above in support of Groups XVI and XVII, Claims 10 and 11, are incorporated hereinbelow in support of Group XIX, Claim 13.

Group XIX, Claim 13, includes the further limitation that the recombinant DNA sequence has the base sequence GGG TCT GGC TGC TTT GGG AGG AAG ATC GAC CGG ATC AGC TCC TCC AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT, the sequence of Group VII, Claim 20. Therefore, the arguments presented above in support of Group VII, Claim 20, are also incorporated hereinbelow in support of Group XIX, Claim 13.

As discussed in support of Group VII, Claim 20, a comparison of the sequence of Groups VII and XIX, Claims 20 and 13, with the base sequence recited from base number 316 through base number 393 in Figure 3 of Maekawa et al shows at least 14 structural differences (i.e., the differences in the sequences as described above for Group XVIII, Claim 12, plus two additional structural differences in the first codon [GGG, whereas the corresponding sequence of Maekawa et al at positions 316-318 is GAC]). Thus, given the structural differences between the base sequence recited in Group XIX, Claim 13, and the closest base sequence recited in the cited

references, Group XIX, Claim 13, is fully and independently patentable over the cited references.

Furthermore, the evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the recombinant DNA sequence of Group XIX, Claim 13, based on the teachings and disclosures of the cited references. In addition, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the recombinant DNA sequence of Group XIX, Claim 13. As discussed above, both Seilhamer et al and Maniatis et al indicate that no unusual problems are expected in screening a genomic library (in accordance with the procedures of Seilhamer et al). The combined teachings of the cited references thus attest to the unforeseen difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al.

The cited references do not suggest that the modifications necessary to arrive at the present polynucleotides from the closest polynucleotide(s) disclosed in or suggested by the cited references are desirable, or would even result in a gene which encodes a functional polypeptide. Thus, Group XIX, Claim 13, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XX -- CLAIM 2

Group XX, Claim 2, concerns a DNA comprising a base sequence encoding a polypeptide possessing natriuretic activity and having the amino acid sequence Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His, the sequence recited in Group III, Claim 16. Therefore, the arguments presented above in support of Groups I and III, Claims 14 and 16, are incorporated hereinbelow in support of Group XX, Claim 2.

As discussed in support of Groups I and III, Claims 14 and 16, for each difference in the amino acid sequence encoded by the DNA of Group XX, Claim 2, and the structurally closest DNA sequence of the cited references (shown in Fig. 3 of Maekawa et al), at least one difference in DNA sequence exists. Consequently, the structure of the recombinant DNA sequence of Group XX, Claim 2, contains at least ten structural differences from the structurally closest polynucleotide suggested by the cited references.

The cited references do not suggest that the differences in structure between the DNA of Group XX, Claim 2, and the structurally closest polynucleotide of the cited references are desirable, or would result in a DNA which encodes a polypeptide possessing natriuretic activity. Consequently, one would not be motivated to make the changes to the

structurally closest polynucleotide suggested by the cited references necessary to arrive at the present DNA.

Even further, the DNA of Group XX, Claim 2, provides a means for obtaining a human natriuretic peptide (hBNP) which is expected to have considerably higher rectum and smooth muscle relaxation activities and greater natriuretic activity than the corresponding hANP, based on the known 3- to 4-fold increase in the rectum relaxation activity of pBNP relative to pANP (see page 2, lines 3-15 of the present specification). Consequently, the DNA of Group XX, Claim 2, represents a significant and meaningful advancement in the treatment of circulatory disease.

The evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the DNA of Group XX, Claim 2, based on the teachings and disclosures of the cited references. Further, the DNA of Group XX, Claim 2, is structurally non-obvious from the closest possible polynucleotide suggested by the cited references. Therefore, the DNA of Group XX, Claim 2, is fully and independently patentable over the cited references.

Furthermore, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the present DNA. Interestingly, as discussed above, both Seilhamer et al and Maniatis et al equate a genomic library with a cDNA library, thereby indicating that no unusual problems are

expected in screening a genomic library. Even more interesting, the temperature conditions used by Seilhamer et al were less stringent (37-42°C; col. 9, lines 6-10 and 38-42) than those used by the present Inventors to obtain the present DNA sequence (60°C; see page 14, line 19 of the present specification).

Therefore, the combined teachings of the cited references attest to the difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al. The cited references do not suggest that the modifications necessary to arrive at the present polynucleotide from the closest polynucleotide(s) disclosed in or suggested by the cited references are desirable, or would even result in a gene which encodes a polypeptide possessing natriuretic activity, a property affirmatively recited in Group XX, Claim 2.

Therefore, Group XX, Claim 2, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XXI -- CLAIM 3

Group XXI, Claim 4, concerns a DNA comprising a base sequence encoding a polypeptide possessing natriuretic activity and having the following amino acid sequence:

His Pro Leu Gly Ser Pro Gly Ser Ala Ser Asp Leu Glu
Thr Ser Gly Leu Gln Glu Gln Arg Asn His Leu Gln Gly
Lys Leu Ser Glu Leu Gln Val Glu Gln Thr Ser Leu Glu
Pro Leu Gln Glu Ser Pro Arg Pro Thr Gly Val Trp Lys
Ser Arg Glu Val Ala Thr Glu Gly Ile Arg Gly His Arg
Lys Met Val Leu Tyr Thr Leu Arg Ala Pro Arg Ser Pro
Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met
Asp Arg Ile Ser Ser Ser Ser Gly Leu

The sequence immediately above is common to both Group XXI, Claim 3, and Group IV, Claim 17. Therefore, the arguments presented above in support of Groups I, III and IV, Claims 14, 16 and 17, are incorporated hereinbelow in support of Group XXI, Claim 3.

As discussed in support of Group IV, Claim 17, the amino acid sequence recited in Group XXI, Claim 3, corresponds to the amino acid sequence disclosed by Maekawa et al from position 26 through position 131 in Figure 3 (page 414). As discussed in support of Group IV, Claim 17, there appear to be more differences than similarities in the codons of the DNA of Group XXI, Claim 3, as compared to the possible codons of the corresponding sequence recited in Figure 3 of Meakawa et al. Thus, the DNA of Group XXI, Claim 3, is structurally non-obvious from the closest possible polynucleotide suggested by the cited references. As a result, the DNA of Group XXI,

Claim 3, is fully and independently patentable over the cited references.

Furthermore, as described above for Groups I, III and IV, Claims 14, 16 and 17, the evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the DNA of Group XXI, Claim 3, based on the teachings and disclosures of the cited references. In addition, the cited references do not suggest that the differences in structure between the DNA of Group XXI, Claim 3, and the structurally closest polynucleotide of the cited references are desirable, or would result in a DNA which encodes a polypeptide possessing natriuretic activity.

Consequently, one would not be motivated to make the changes to the structurally closest polynucleotide suggested by the cited references necessary to arrive at the present DNA.

Even further, the DNA of Group XXI, Claim 3, provides a means for obtaining a human natriuretic peptide (hBNP) which is expected to have considerably higher rectum and smooth muscle relaxation activities and greater natriuretic activity than the corresponding hANP, based on the known 3- to 4-fold increase in the rectum relaxation activity of pBNP relative to pANP (see page 2, lines 3-15 of the present specification). Consequently, the DNA of Group XXI, Claim 3, represents a significant and meaningful advancement in the treatment of circulatory disease.

The evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the DNA of Group XXI, Claim 3, based on the teachings and disclosures of the cited references. Further, the DNA of Group XXI, Claim 3, is structurally non-obvious from the closest possible polynucleotide suggested by the cited references. Therefore, the DNA of Group XXI, Claim 3, is fully and independently patentable over the cited references.

Furthermore, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the present DNA. Therefore, the combined teachings of the cited references attest to the difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al.

Therefore, Group XXI, Claim 3, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XXII -- CLAIM 4

Group XXII, Claim 4, concerns a DNA comprising a base sequence encoding a polypeptide possessing natriuretic activity and having the following amino acid sequence:

Met Asp Pro Gln Thr Ala Pro Ser Arg Ala Leu Leu Leu Leu
Phe Leu His Leu Ala Phe Leu Gly Gly Arg Ser His Pro Leu
Gly Ser Pro Gly Ser Ala Ser Asp Leu Glu Thr Ser Gly Leu
Gln Glu Gln Arg Asn His Leu Gln Gly Lys Leu Ser Glu Leu
Gln Val Glu Gln Thr Ser Leu Glu Pro Leu Gln Glu Ser Pro
Arg Pro Thr Gly Val Trp Lys Ser Arg Glu Val Ala Thr Glu
Gly Ile Arg Gly His Arg Lys Met Val Leu Tyr Thr Leu Arg
Ala Pro Arg Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly
Cys Lys Val Leu Arg Arg His

The sequence immediately above is common to Group XXII, Claim 4, and Group V, Claim 18. Therefore, the arguments presented above in support of Groups I, III, IV and V, Claims 14, 16, 17 and 18, are incorporated hereinbelow in support of Group XXII, Claim 4.

As discussed in support of Group V, Claim 18, the amino acid sequence recited in Group XXII, Claim 4, corresponds to the amino acid sequence disclosed by Maekawa et al from position 1 through position 131 in Figure 3 (page 414). As discussed in support of Groups IV and V, Claims 17 and 18, there appear to be more differences than similarities in the codons of the DNA of Group XXII, Claim 4, as compared to the possible codons of the corresponding sequence recited in Figure 3 of Meakawa et al. Thus, the DNA of Group XXII, Claim 4, is structurally non-obvious from the closest possible

polynucleotide suggested by the cited references. As a result, the DNA of Group XXII, Claim 4, is fully and independently patentable over the cited references.

Furthermore, as described above for Groups I, III, IV and V, Claims 14, 16, 17 and 18, the evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the DNA of Group XXII, Claim 4, based on the teachings and disclosures of the cited references. In addition, the cited references do not suggest that the differences in structure between the DNA of Group XXII, Claim 4, and the structurally closest polynucleotide of the cited references are desirable, or would result in a DNA which encodes a polypeptide possessing natriuretic activity.

Consequently, one would not be motivated to make the changes to the structurally closest polynucleotide suggested by the cited references necessary to arrive at the present DNA.

Even further, the DNA of Group XXII, Claim 4, provides a means for obtaining a human natriuretic peptide (hBNP) which is expected to have considerably higher rectum and smooth muscle relaxation activities and greater natriuretic activity than the corresponding hANP, based on the known 3- to 4-fold increase in the rectum relaxation activity of pBNP relative to pANP (see page 2, lines 3-15 of the present specification). Consequently, the DNA of Group XXII, Claim 4, represents a significant and meaningful advancement in the treatment of circulatory disease.

The evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the DNA of Group XXII, Claim 4, based on the teachings and disclosures of the cited references. Further, the DNA of Group XXII, Claim 4, is structurally non-obvious from the closest possible polynucleotide suggested by the cited references. Therefore, the DNA of Group XXII, Claim 4, is fully and independently patentable over the cited references.

Furthermore, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the present DNA. Therefore, the combined teachings of the cited references attest to the difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al.

Therefore, Group XXII, Claim 4, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XXIII -- CLAIM 5

Group XXIII, Claim 5, depends from Group XX, Claim 2. Therefore, Group XXIII, Claim 5, includes all of the limitations of Group XX, Claim 2, and all arguments presented above in support of Group XX, Claim 2, are incorporated hereinbelow in support of Group XXIII, Claim 5.

Group XXIII, Claim 5, includes the further limitation that the DNA has the base sequence

AGC CCC AAG ATG GTG CAA GGG TCT GGC TGC TTT

GGG AGG AAG ATG GAC CGG ATC AGC TCC TCC AGT

GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT,

a sequence common to both Group XXIII, Claim 5, and Group VIII, Claim 21. Therefore, the arguments presented above in support of Groups I, III and VIII, Claims 14, 16 and 21, are incorporated hereinbelow in support of Group XXIII, Claim 5.

As discussed in support of Group VIII, Claim 21, the sequence recited in Group XXIII, Claim 5, corresponds to the sequence disclosed by Maekawa et al from base positions 298 through 394 in Figure 3 (page 414). There are a minimum of 18 structural differences between the cDNA of Group XXIII, Claim 5, and the structurally closest sequence disclosed by the cited references. Therefore, Group XXIII, Claim 5, is fully and independently patentable over the cited references.

Furthermore, as described above for Groups I, III and VIII, Claims 14, 16 and 21, the evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the DNA of Group XXIII, Claim 5, based on the teachings and disclosures of the cited references. In addition, the cited references do not suggest that the differences in structure between the DNA of Group XXIII, Claim 5, and the structurally closest polynucleotide of the cited references are desirable, or would result in a DNA which

encodes a polypeptide possessing natriuretic activity.

Consequently, one would not be motivated to make the changes to the structurally closest polynucleotide suggested by the cited references necessary to arrive at the present DNA.

Even further, the DNA of Group XXIII, Claim 5, provides a means for obtaining a human natriuretic peptide (hBNP) which is expected to have considerably higher rectum and smooth muscle relaxation activities and greater natriuretic activity than the corresponding hANP, based on the known 3- to 4-fold increase in the rectum relaxation activity of pBNP relative to pANP (see page 2, lines 3-15 of the present specification). Consequently, the DNA of Group XXIII, Claim 5, represents a significant and meaningful advancement in the treatment of circulatory disease.

The evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the DNA of Group XXIII, Claim 5, based on the teachings and disclosures of the cited references. Further, the DNA of Group XXIII, Claim 5, is structurally non-obvious from the closest possible polynucleotide suggested by the cited references. Therefore, the DNA of Group XXIII, Claim 5, is fully and independently patentable over the cited references.

Furthermore, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the present DNA. Therefore, the combined teachings of the cited

references attest to the difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al.

Therefore, Group XXIII, Claim 5, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XXIV -- CLAIM 6

Group XXIV, Claim 6, depends from Group XXI, Claim 3. Therefore, Group XXIV, Claim 6, includes all of the limitations of Group XXI, Claim 3, and all arguments presented above in support of Group XXI, Claim 3, are incorporated hereinbelow in support of Group XXIV, Claim 6.

Group XXIV, Claim 6, includes the further limitation that the DNA has the base sequence:

CAC CCG CTG GGC AGC CCC GGT TCA GCC TCG GAC TTG GAA ACG
TCC GGG TTA CAG GAG CAG CGC AAC CAT TTG CAG GGC AAA CTG
TCG GAG CTG CAG GTG GAG CAG ACA TCC CTG GAG CCC CTC CAG
GAG AGC CCC CGT CCC ACA GGT GTC TGG AAG TCC CGG GAG GTA
GCC ACC GAG GGC ATC CGT GGG CAC CGC AAA ATG CTC CTC TAC
ACC CTG CGG GCA CCA CGA AGC CCC AAG ATG GTG CAA GGG TCT
GGC TGC TTT GGG AGG AAG ATG GAC CGG ATC AGC TCC TCC AGT
GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT,

a sequence common to both Group XXIV, Claim 6, and Group IX, Claim 22. Therefore, the arguments presented above in support

of Groups I, III, IV, VIII and IX, Claims 14, 16, 17, 21 and 22, are also incorporated hereinbelow in support of Group XXIV, Claim 6.

As discussed in support of Group IX, Claim 22, the sequence recited in Group XXIV, Claim 6, corresponds to the sequence disclosed by Maekawa et al from base positions 67 through 394. A comparison of these sequences reveals structural differences in the vast majority of the codons, many codons differing in more than one position. One of ordinary skill would have little expectation that the nucleotide disclosed by Maekawa et al would be likely to suggest or lead to the DNA of Group XXIV, Claim 6. Therefore, Group XXIV, Claim 6, is fully and independently patentable over the cited references.

Furthermore, as described above for Groups I, III, IV, VIII and IX, Claims 14, 16, 17, 21 and 22, the evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the DNA of Group XXIV, Claim 6, based on the teachings and disclosures of the cited references. In addition, the cited references do not suggest that the differences in structure between the DNA of Group XXIV, Claim 6, and the structurally closest polynucleotide of the cited references are desirable, or would result in a DNA which encodes a polypeptide possessing natriuretic activity. Consequently, one would not be motivated to make the changes

to the structurally closest polynucleotide suggested by the cited references necessary to arrive at the present DNA.

Even further, the DNA of Group XXIV, Claim 6, provides a means for obtaining a human natriuretic peptide (hBNP) which is expected to have considerably higher rectum and smooth muscle relaxation activities and greater natriuretic activity than the corresponding hANP, based on the known 3- to 4-fold increase in the rectum relaxation activity of pBNP relative to pANP (see page 2, lines 3-16 of the present specification). Consequently, the DNA of Group XXIV, Claim 6, represents a significant and meaningful advancement in the treatment of circulatory disease.

The evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the DNA of Group XXIV, Claim 6, based on the teachings and disclosures of the cited references. Further, the DNA of Group XXIV, Claim 6, is structurally non-obvious from the closest possible polynucleotide suggested by the cited references. Therefore, the DNA of Group XXIV, Claim 6, is fully and independently patentable over the cited references.

Furthermore, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the present DNA. Therefore, the combined teachings of the cited references attest to the difficulties encountered in arriving

at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al.

Therefore, Group XXIV, Claim 6, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XXV -- CLAIM 7

Group XXV, Claim 7, depends from Group XXII, Claim 4. Therefore, Group XXV, Claim 7, includes all of the limitations of Group XXII, Claim 4, and all arguments presented above in support of Group XXII, Claim 4, are incorporated hereinbelow in support of Group XXV, Claim 7.

Group XXV, Claim 7, includes the further limitation that the DNA has the base sequence:

ATG GAT CCC CAG ACA GCA CCT TCC CGG GCG CTC CTG CTC CTG
CTC TTC TTG CAT CTG GCT TTC CTG GGA GGT CGT TCC CAC CCG
CTG GGC AGC CCC GGT TCA GCC TCG GAC TTG GAA ACG TCC GGG
TTA CAG GAG CAG CGC AAC CAT TTG CAG GGC AAA CTG TCG GAG
CTG CAG GTG GAG CAG ACA TCC CTG GAG CCC CTC CAG GAG AGC
CCC CGT CCC ACA GGT GTC TGG AAG TCC CGG GAG GTA GCC ACC
GAG GGC ATC CGT GGG CAC CGC AAA ATG GTC CTC TAC ACC CTG
CGG GCA CCA CGA AGC CCC AAG ATG GTG CAA GGG TCT GGC TGC
TTT GGG AGG AAG ATG GAC CGG ATC AGC TCC TCC AGT GGC CTG
GGC TGC AAA GTG CTG AGG CGG CAT,

a sequence common to both Group XXV, Claim 7, and Group X, Claim 23. Therefore, the arguments presented above in support of Groups I, III, IV, V, VIII, IX and X, Claims 14, 16, 17, 18, 21, 22 and 23, are also incorporated hereinbelow in support of Group XXV, Claim 7.

As discussed in support of Group X, Claim 23, the sequence recited in Group XXV, Claim 7, corresponds to the sequence disclosed by Maekawa et al from base positions 1 through 394. A comparison of these sequences reveals structural differences in the vast majority of the codons, many codons differing in more than one position. One of ordinary skill would have little expectation that the nucleotide disclosed by Maekawa et al would be likely to suggest or lead to the DNA of Group XXV, Claim 7. Therefore, Group XXV, Claim 7, is fully and independently patentable over the cited references.

Furthermore, as described above for Groups I, III, IV, V, VIII, IX and X, Claims 14, 16, 17, 18, 21, 22 and 23, the evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the DNA of Group XXV, Claim 7, based on the teachings and disclosures of the cited references. In addition, the cited references do not suggest that the differences in structure between the DNA of Group XXV, Claim 7, and the structurally closest polynucleotide of the cited references are desirable, or would result in a DNA which encodes a polypeptide possessing

natriuretic activity. Consequently, one would not be motivated to make the changes to the structurally closest polynucleotide suggested by the cited references necessary to arrive at the present DNA.

Even further, the DNA of Group XXV, Claim 7, provides a means for obtaining a human natriuretic peptide (hBNP) which is expected to have considerably higher rectum and smooth muscle relaxation activities and greater natriuretic activity than the corresponding hANP, based on the known 3- to 4-fold increase in the rectum relaxation activity of pBNP relative to pANP (see page 2, lines 3-16 of the present specification). Consequently, the DNA of Group XXV, Claim 7, represents a significant and meaningful advancement in the treatment of circulatory disease.

The evidence of record clearly establishes that no reasonable expectation of success existed in arriving at the DNA of Group XXV, Claim 7, based on the teachings and disclosures of the cited references. Further, the DNA of Group XXV, Claim 7, is structurally non-obvious from the closest possible polynucleotide suggested by the cited references. Therefore, the DNA of Group XXV, Claim 7, is fully and independently patentable over the cited references.

Furthermore, the clear failure of Seilhamer et al to successfully achieve the result obtained by the present Inventors also attests to the nonobviousness of the present DNA. Therefore, the combined teachings of the cited

references attest to the difficulties encountered in arriving at the present invention, as described (1) in the Declaration of Sudoh and (2) by Seilhamer et al.

Therefore, Group XXV, Claim 7, is fully and independently patentable over the cited references. As a result, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XXVI -- CLAIM 30

Group XXVI, Claim 30, concerns a method of producing cDNA, comprising:

hybridizing a probe having a DNA sequence encoding a part of porcine brain natriuretic peptide to a human cDNA library;

selecting a positive clone; and

isolating the cDNA of the positive clone.

The present method thus results in production of cDNA encoding human brain natriuretic peptide (hBNP).

As discussed above, Maekawa et al disclose the cloning and sequence analysis of cDNA encoding a precursor for porcine brain natriuretic peptide (pBNP). Sudoh et al (R) disclose the sequences of porcine BNP. Sudoh et al (T) disclose a 32-amino acid-long brain natriuretic peptide identified in porcine brain. Oikawa et al disclose the structure of dog and rabbit precursors of atrial natriuretic peptides (ANP's) deduced from nucleotide sequences of cloned cDNA. Vlasuk et

al disclose the structure and analysis of the bovine atrial natriuretic peptide (bANP) precursor gene. Thus, the differences between the invention of Group XXVI, Claim 30, and the disclosures of these references lie primarily in the species of organism (human) from which a cDNA library was prepared for the hybridizing step, and use of a probe having a DNA sequence encoding a part of porcine brain natriuretic peptide as a screening tool.

On page 228, Maniatis et al teach a method for identifying cDNA clones corresponding to developmentally regulated mRNAs. A population of cDNA molecules enriched in sequences characteristic for a particular developmental stage is used to probe a cDNA or genomic library.

Given the equivalence of a cDNA and a genomic library taught by Maniatis et al on page 228, it is not clear how Maniatis et al cure the failure of Seilhamer et al (discussed above) to successfully isolate human DNA encoding a BNP using porcine cDNA. Maniatis et al suggest that the same result is obtainable using either a cDNA or a genomic library. Thus, if one cannot achieve success with one library, Maniatis et al does not lead one to expect success using the other library.

Furthermore, the procedure of Maniatis et al appears to require use of a probe from the same tissue and the same species. For example, on page 227, Maniatis et al teach that differential hybridization (the technique relied upon by the Examiner) is used when mRNA preparations are available which

contain many sequences in common, except for the presence or absence of a few species of interest. Differential hybridization is taught as being useful for identifying certain mRNAs which may be present in a particular sample in which production of the mRNA has been induced (e.g., by heat shock, drugs, hormones or a particular substrate). This strongly suggests that the genetic material for each of the mRNA preparations comes from the same source, but is treated differently in one of the preparations so as to induce the formation of a particular mRNA in that preparation.

Maniatis et al neither teach nor suggest that success can be achieved employing cDNA from one species to identify the inducible genes from a second species. Thus, the technique of differential hybridization appears to be relevant to obtaining a clone from the same species, based on the teachings of Maniatis et al immediately preceding the disclosure relied upon for the present rejection.

In the disclosure relied upon for the present rejection, Maniatis et al teach that cDNA prepared from mRNA obtained at one developmental stage (stage 1) is hybridized to a 20-fold excess of mRNA obtained from another stage (stage 2), and the hybrid is removed. This procedure of Maniatis et al is then repeated twice more using a 50-100-fold excess of stage 2 mRNA. The unbound cDNA fraction is then hybridized to a 100-fold excess of stage 1 mRNA, and the hybrid is recovered.

After removing the mRNA, the cDNA that is highly enriched in stage 1-specific sequences is used as a probe.

One would not reasonably expect success using the procedure described by Maniatis et al on page 228 if a probe from a different species is used. If mRNA from a different organism is used, the polynucleotide homology differences between the two organisms may be sufficiently great as to prevent hybridization, particularly since the two mRNA preparations are obtained from different developmental stages. A difference in the developmental stages induces differences in mRNAs, even when obtained from the same organism or cell. To minimize the differences between the two mRNAs and thus maximize the chances of success (note the prior teaching of Maniatis et al that the two mRNA preparations contain many sequences in common, but differ from each other based on the presence or absence of a few species of interest), it is apparent that Maniatis et al refer to mRNA obtained from different developmental stages of the same organism.

Based on the steps recited in the method of Group XXVI, Claim 30, one must screen a human cDNA library using a probe from a different species. The rejection cannot be properly based on use of a porcine DNA probe to hybridize to human DNA, because the cited references disclose only the failure of porcine DNA probe to hybridize to human DNA.

Furthermore, in the present method, a human cDNA library is screened using a DNA fragment encoding porcine BNP (see,

for example, page 14, lines 1-12 of the present specification). Positive plaques were thus obtained and isolated (page 15, lines 2-3). Accordingly, the relevance of differential hybridization, the process of Maniatis et al identified by the Examiner as being the most pertinent process, is not understood.

Consequently, it is not seen how the teachings of Maniatis et al cure the deficiencies of the remaining cited references. The method of Maniatis et al appears to require that a probe from the same cell (i.e., the same tissue and the same species) be used. Further, there is no evidence that the method of Maniatis et al relied upon by the Examiner is reasonably likely to be successful in arriving at the present invention from the closest polynucleotides disclosed or suggested by the cited references. Consequently, the method of Group XXVI, Claim 30, is fully and independently patentable over the cited references.

However, assuming *arguendo* that it would have been obvious for one of ordinary skill in the art to use the porcine DNA sequence disclosed by Maekawa et al, or an effective portion thereof (as taught by Seilhamer et al [col. 8, lines 40-54]), as a probe to screen for the human BNP gene, the factual bases by which one of ordinary skill evaluates the expectation of success do not establish that one would have had a reasonable expectation of success in arriving at the present invention from the teachings of the cited references

(see the Declaration of Sudoh dated October 12, 1994 and filed October 20, 1994). Thus, the evidence of record supports the patentability of the present method.

For example, neither (1) the 70% degree of homology between human atrial natriuretic peptide (hANP) and porcine BNP (pBNP) taught by Sudoh et al (R) and (T) nor (2) the 50.6-65.7% degree of homology between hANP mRNA and pBNP mRNA taught by Maekawa et al is sufficiently high for one of ordinary skill to reasonably expect success in cloning and isolating the cDNA of one based on the sequence of the other (see paragraph 5, page 3 of the Declaration of Sudoh dated October 12, 1994 and filed October 20, 1994). In the present case, "cloning and isolating" using a probe requires hybridizing the probe to a DNA library.

Further, Table 1 of Oikawa et al teaches that the homology between hANP and other mammalian ANPs is only 52-60%. Thus, assuming that one of ordinary skill expects the same degree of homology between hBNP and other mammalian BNPs as is observed between hANP and other mammalian ANPs, Sudoh et al (R) and (T), Maekawa et al and Oikawa et al appear to indicate that the degree of homology is greater between pBNP and hANP than what one expects between pBNP and hBNP. As a result, one might expect a probe based on the pBNP gene to lead to cloning of a hANP gene, rather than a hBNP gene (see paragraph 6, pages 3-4 of the Declaration).

In addition, Sudoh et al (*Biochem. Biophys. Res. Comm.*, 159:1427-1434, submitted with and incorporated into the Declaration by reference) disclose that human and porcine ANP's have 89.7% and 100% identical residues in the pro-form and α -form, respectively (page 1433, lines 1-3). However, the high homology between the pro- and α -forms of hANP and pANP would lead one to reasonably expect success in cloning and isolating hBNP cDNA using a 10-20 bp pBNP probe, which the present Inventors attempted to do, but failed to successfully carry out (see paragraph 7, page 4 of the Declaration).

Thus, in addition to the failure of Seilhamer et al to isolate a polynucleic acid encoding hBNP using a porcine cDNA probe, the present Inventors also failed to obtain human BNP cDNA using a 10-20 bp pBNP probe. The failure of others to produce the claimed invention, and the arrival at a solution to unexpected and unforeseen problems have long been considered objective indicia of the non-obviousness of an invention. See Graham v. John Deere, 383 U.S. 1, 148 U.S.P.Q. 459 (1966); Eibel Process Co. v. Minnesota & Ontario Paper Co., 261 U.S. 45, 43 S.Ct. 322 (1923); and Reeves Instrument Corp. v. Beckman Instruments, Inc., 444 F.2d 263, 170 U.S.P.Q. 74 (9th Cir. 1971), cert. denied, 404 U.S. 751 (1971).

Furthermore, the low homology (70.0%) between human prepro-BNP and porcine prepro-BNP (results determined by the present Inventors, disclosed by Sudoh et al [*Biochem. Biophys. Res. Comm.*, 159:1427-1434]) presents a sharp contrast to the

more highly conserved mammalian ANP's, thus introducing a further unexpected problem in cloning hBNP. This unexpected problem makes it surprising that hBNP cDNA could be cloned and isolated, given the level of ordinary skill and the knowledge in this field at the time of filing grandparent U.S. application Serial No. 07/486,827 (March 1, 1990) (see paragraph 9, page 4 of the Declaration of Sudoh).

Therefore, one of ordinary skill would not have had a reasonable expectation of success for the present method from the knowledge present in the art at the time grandparent application Serial No. 07/486,827 was filed.

Finally, as discussed above, Seilhamer et al disclose that no conditions could be determined under which the cDNA encoding porcine BNP would hybridize to human DNA, even though there was every reason to believe that it would (see col. 8, lines 40-54 and col. 9, lines 32-35 and 45-47 of Seilhamer et al). Seilhamer et al did, however, successfully use the pBNP cDNA to retrieve genes encoding related proteins from other species, such as a pig, a rat, a dog, a cat and a rabbit (col. 9, lines 32-44).

Since Seilhamer et al successfully used the pBNP cDNA to retrieve the corresponding genes from five out of six species attempted, the assertion in the Official Action of February 6, 1995 (see page 4, lines 12-19) that it is not surprising that Seilhamer et al fail to isolate the human BNP genomic clone appears to be a hindsight reconstruction, rather than an

accurate interpretation of the teachings of Seilhamer et al.
In fact, Seilhamer et al specifically disclose:

"There was every reason to believe that porcine BNP should be capable of hybridizing to human NRP under appropriate conditions; however no conditions could be determined under which pBNP would hybridize to a human library. This was surprising in that, in an evolutionary sense, porcine BNP is more likely to be related to the corresponding human protein, than is a corresponding canine protein. It was thus unexpected that porcine BNP was unable to identify human NRP...." (col. 8, lines 44-54; emphasis added).

Consequently, the conclusion in the Official Action of February 6, 1995, that it is not surprising that Seilhamer et al failed to isolate the human BNP genomic clone using pBNP cDNA is not accurate since Seilhamer et al themselves state that is surprising. As a result, the success of the present Inventors in obtaining DNA encoding human BNP is surprising and unexpected, particularly in view of the failure of Seilhamer et al to hybridize DNA encoding pBNP to human DNA.

Thus, the method of Group XXVI, Claim 30, is not obvious in view of the cited references, based on the evidence of record. As a further result, Group XXVI, Claim 30, is fully and independently patentable over the cited references. Therefore, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XXVII -- CLAIMS 31 and 32

Group XXVII, Claims 31 and 32, depends from Group XXVI, Claim 30. Therefore, Group XXVII, Claims 31 and 32, includes all of the limitations of Group XXVI, Claim 30, and all arguments presented above in support of Group XXVI, Claim 30, are incorporated hereinbelow in support of Group XXVII, Claims 31 and 32.

Group XXVII, Claim 31, includes the further limitation that the cDNA (the product of the method) encodes human brain natriuretic peptide. (Claim 32 depends from Claim 31, and includes the further limitation that the probe is labelled.) As discussed above in support of Group XXVI, Claim 30, one of ordinary skill would not have had a reasonable expectation of success in arriving at the present invention from the teachings of the cited references (see the Declaration of Sudoh dated October 12, 1994 and filed October 20, 1994). Thus, the evidence of record supports the patentability of the present method.

For example, neither (1) the 70% degree of homology between human atrial natriuretic peptide (hANP) and porcine BNP (pBNP) taught by Sudoh et al (R) and (T) nor (2) the 50.6-65.7% degree of homology between hANP mRNA and pBNP mRNA taught by Maekawa et al is sufficiently high for one of ordinary skill to reasonably expect success in cloning and isolating cDNA encoding human BNP based on the sequence of DNA encoding porcine BNP (see paragraph 5, page 3 of the

Declaration of Sudoh dated October 12, 1994 and filed October 20, 1994).

Further, assuming that one of ordinary skill expects the same degree of homology between hBNP and other mammalian BNPs as is observed between hANP and other mammalian ANPs, Sudoh et al (R) and (T), Maekawa et al and Oikawa et al appear to indicate that one might expect a probe based on the pBNP gene to lead to cloning of a hANP gene, rather than a hBNP gene, as is affirmatively recited in Group XXVII, Claim 31 (see paragraph 6, pages 3-4 of the Declaration).

In addition to the failure of Seilhamer et al to isolate a polynucleic acid encoding hBNP using a porcine cDNA probe, the present Inventors also failed to obtain human BNP cDNA using a 10-20 bp pBNP probe. The failure of others to produce the claimed invention, and the arrival at a solution to unexpected and unforeseen problems have long been considered objective indicia of the non-obviousness of an invention. See Graham v. John Deere, 383 U.S. 1, 148 U.S.P.Q. 459 (1966); Eibel Process Co. v. Minnesota & Ontario Paper Co., 261 U.S. 45, 43 S.Ct. 322 (1923); and Reeves Instrument Corp. v. Beckman Instruments, Inc., 444 F.2d 263, 170 U.S.P.Q. 74 (9th Cir. 1971), cert. denied, 404 U.S. 751 (1971).

Furthermore, the low homology (70.0%) between human prepro-BNP and porcine prepro-BNP (results determined by the present Inventors, disclosed by Sudoh et al [*Biochem. Biophys. Res. Comm.*, 159:1427-1434]) presents a sharp contrast to the

more highly conserved mammalian ANP's, thus introducing a further unexpected problem in cloning hBNP. This unexpected problem makes it surprising that the result specifically recited in Group XXVII, Claim 31 (production of hBNP cDNA), could be obtained, given the level of ordinary skill and the knowledge in this field at the time of filing grandparent U.S. application Serial No. 07/486,827 (March 1, 1990) (see paragraph 9, page 4 of the Declaration of Sudoh).

Therefore, one of ordinary skill would not have had a reasonable expectation of success for the method of Group XXVII, Claims 31 and 32, from the knowledge present in the art at the time grandparent application Serial No. 07/486,827 was filed.

Finally, as discussed above, Seilhamer et al disclose their complete failure to hybridize cDNA encoding porcine BNP to human DNA, even though there was every reason to believe that it would succeed (see col. 8, lines 40-54 and col. 9, lines 32-35 and 45-47 of Seilhamer et al). In fact, Seilhamer et al specifically state:

"There was every reason to believe that porcine BNP should be capable of hybridizing to human NRP under appropriate conditions; however no conditions could be determined under which pBNP would hybridize to a human library. This was surprising in that, in an evolutionary sense, porcine BNP is more likely to be related to the corresponding human protein, than is a corresponding canine protein. It was thus unexpected that porcine BNP was unable to identify human NRP...." (col. 8, lines 44-54; emphasis added).

Consequently, the conclusion in the Official Action of February 6, 1995, that it is not surprising that Seilhamer et al failed to isolate the human BNP genomic clone using pBNP cDNA is not accurate since Seilhamer et al themselves state that is surprising. As a result, the success of the present Inventors in obtaining DNA encoding human BNP is surprising and unexpected, particularly in view of the failure of Seilhamer et al to hybridize DNA encoding pBNP to human DNA. Thus, the method of Group XXVI, Claim 30, is not obvious in view of the cited references, based on the evidence of record.

Thus, the method of Group XXVII, Claims 31 and 32, is not obvious in view of the cited references, based on the evidence of record. As a further result, Group XXVII, Claims 31 and 32, is fully and independently patentable over the cited references. Therefore, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XXVIII -- CLAIM 33

Group XXVIII, Claim 33, depends from Group XXVII, Claim 31. Therefore, Group XXVIII, Claim 33, includes all of the limitations of Group XXVII, Claim 31, and all arguments presented above in support of Group XXVII, Claim 31, are incorporated hereinbelow in support of Group XXVIII, Claim 33.

Group XXVIII, Claim 33, includes the further limitation that the probe is obtained by digesting a complete or incomplete cDNA clone encoding porcine brain natriuretic

peptide with endonucleases XhoI and RsaI, a limitation common to Group XXVIII, Claim 33, and Group XIII, Claims 26 and 28. Therefore, all arguments presented above in support of Groups I, XI, XII and XIII, Claims 14, 24, 25, 26 and 28, are incorporated hereinbelow in support of Group XXVIII, Claim 33.

As discussed above in support of Group XIII, Claims 26 and 28, the only disclosure in the cited references relevant to the distinguishing limitation of Group XXVIII, Claim 33, is by Oikawa et al, who suggest cleaving dog and rabbit cDNA encoding atrial natriuretic polypeptides with RsaI. However, the cited references are silent with regard to preparing a probe by either (1) digesting any DNA encoding a porcine natriuretic peptide or a brain natriuretic peptide, or (2) digesting any DNA with XhoI.

Consequently, the cited references cannot suggest obtaining a probe by digesting a complete or incomplete cDNA clone encoding porcine brain natriuretic peptide with endonucleases XhoI and RsaI. As a result, the method of Group XXVIII, Claim 33, is fully and independently patentable over the cited references. Therefore, this ground of rejection is clearly in error, and should be withdrawn.

Furthermore, as discussed above in support of Groups I, XI, XII and XXVII, Claims 14, 24, 25 and 30, one of ordinary skill would not have had a reasonable expectation of success in arriving at the present invention from the teachings of the cited references (see the Declaration of Sudoh dated October

12, 1994 and filed October 20, 1994). Thus, the evidence of record supports the patentability of the present method.

For example, neither (1) the 70% degree of homology between human atrial natriuretic peptide (hANP) and porcine BNP (pBNP) taught by Sudoh et al (R) and (T) nor (2) the 50.6-65.7% degree of homology between hANP mRNA and pBNP mRNA taught by Maekawa et al is sufficiently high for one of ordinary skill to reasonably expect success in cloning and isolating cDNA encoding human BNP based on the sequence of DNA encoding porcine BNP (see paragraph 5, page 3 of the Declaration of Sudoh dated October 12, 1994 and filed October 20, 1994).

Further, assuming that one of ordinary skill expects the same degree of homology between hBNP and other mammalian BNPs as is observed between hANP and other mammalian ANPs, Sudoh et al (R) and (T), Maekawa et al and Oikawa et al appear to indicate that one might expect a probe based on the pBNP gene to lead to cloning of a hANP gene, rather than a hBNP gene (see paragraph 6, pages 3-4 of the Declaration).

In addition to the failure of Seilhamer et al to isolate a polynucleic acid encoding hBNP using a porcine cDNA probe, the present Inventors also failed to obtain human BNP cDNA using a 10-20 bp pBNP probe. The failure of others to produce the claimed invention, and the arrival at a solution to unexpected and unforeseen problems have long been considered objective indicia of the non-obviousness of an invention. See

Graham v. John Deere, 383 U.S. 1, 148 U.S.P.Q. 459 (1966); Eibel Process Co. v. Minnesota & Ontario Paper Co., 261 U.S. 45, 43 S.Ct. 322 (1923); and Reeves Instrument Corp. v. Beckman Instruments, Inc., 444 F.2d 263, 170 U.S.P.Q. 74 (9th Cir. 1971), cert. denied, 404 U.S. 751 (1971).

Furthermore, the low homology (70.0%) between human prepro-BNP and porcine prepro-BNP (results determined by the present Inventors, disclosed by Sudoh et al [*Biochem. Biophys. Res. Comm.*, 159:1427-1434]) presents a sharp contrast to the more highly conserved mammalian ANP's, thus introducing a further unexpected problem in cloning hBNP. This unexpected problem makes it surprising that the method of Group XXVIII, Claim 33 (concerning production of hBNP cDNA), could be obtained, given the level of ordinary skill and the knowledge in this field at the time of filing grandparent U.S. application Serial No. 07/486,827 (March 1, 1990) (see paragraph 9, page 4 of the Declaration of Sudoh).

Therefore, one of ordinary skill would not have had a reasonable expectation of success for the method of Group XXVIII, Claim 33, from the knowledge present in the art at the time grandparent application Serial No. 07/486,827 was filed.

Finally, as discussed above, Seilhamer et al disclose their complete failure to hybridize cDNA encoding porcine BNP to human DNA, even though there was every reason to believe that it would succeed (see col. 8, lines 40-54 and col. 9,

lines 32-35 and 45-47 of Seilhamer et al). In fact, Seilhamer et al specifically state:

"There was every reason to believe that porcine BNP should be capable of hybridizing to human NRP under appropriate conditions; however no conditions could be determined under which pBNP would hybridize to a human library. This was surprising in that, in an evolutionary sense, porcine BNP is more likely to be related to the corresponding human protein, than is a corresponding canine protein. It was thus unexpected that porcine BNP was unable to identify human NRP...." (col. 8, lines 44-54; emphasis added).

Consequently, the conclusion in the Official Action of February 6, 1995, that it is not surprising that Seilhamer et al failed to isolate the human BNP genomic clone using pBNP cDNA is not accurate since Seilhamer et al themselves state that is surprising. As a result, the success of the present Inventors in obtaining DNA encoding human BNP is surprising and unexpected, particularly in view of the failure of Seilhamer et al to hybridize DNA encoding pBNP to human DNA. Thus, the method of Group XXVIII, Claim 33, is not obvious in view of the cited references, based on the evidence of record.

Accordingly, Group XXVIII, Claim 33, is fully and independently patentable over the cited references. Therefore, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XXIX -- CLAIM 34

Group XXIX, Claim 34, depends from Group XXVIII, Claim 33. Therefore, Group XXIX, Claim 34, includes all of the limitations of Group XXVIII, Claim 33, and all arguments presented above in support of Group XXVIII, Claim 33, are incorporated hereinbelow in support of Group XXIX, Claim 34.

Group XXIX, Claim 34, includes the further limitation that the probe encodes the amino acid sequence H-Gly Ser Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His-OH, a sequence commonly recited in Groups II, XIV, XVII and XXIX, Claims 15, 27, 11 and 34. Therefore, all arguments presented above in support of Groups I, II, XI, XII, XIII, XIV and XVII are incorporated hereinbelow in support of Group XXIX, Claim 34.

As discussed above in support of Groups II, XIV and XVII, Claims 15, 27 and 11, in addition to the differences in the codons encoding the amino acids at positions 14, 15, 19, 21, 27 and 32 of pBNP-32, the sequence recited in Group XXIX, Claim 34, contains a structurally different codon encoding the first amino acid of the sequence (corresponding to the position 7 of pBNP-32). Thus, the method of Group XXIX, Claim 34, is not obvious from the cited references in view of the minimum of seven structural differences between the sequence recited therein and closest possible polynucleotide suggested by the cited references.

Furthermore, as discussed above in support of Groups I, II, XI, XII, XIII, XIV, XVII, XXVII and XXVIII, Claims 14, 15, 24, 25, 26, 27, 28, 11, 30, 31, 32 and 33, one of ordinary skill would not have had a reasonable expectation of success in arriving at the present invention from the teachings of the cited references (see the Declaration of Sudoh dated October 12, 1994 and filed October 20, 1994). Thus, the evidence of record supports the patentability of the present method.

For example, neither (1) the 70% degree of homology between human atrial natriuretic peptide (hANP) and porcine BNP (pBNP) taught by Sudoh et al (R) and (T) nor (2) the 50.6-65.7% degree of homology between hANP mRNA and pBNP mRNA taught by Maekawa et al is sufficiently high for one of ordinary skill to reasonably expect success in cloning and isolating cDNA encoding human BNP based on the sequence of DNA encoding porcine BNP (see paragraph 5, page 3 of the Declaration of Sudoh dated October 12, 1994 and filed October 20, 1994).

Further, assuming that one of ordinary skill expects the same degree of homology between hBNP and other mammalian BNPs as is observed between hANP and other mammalian ANPs, Sudoh et al (R) and (T), Maekawa et al and Oikawa et al appear to indicate that one might expect a probe based on the pBNP gene to lead to cloning of a hANP gene, rather than a hBNP gene (see paragraph 6, pages 3-4 of the Declaration).

In addition to the failure of Seilhamer et al to isolate a polynucleic acid encoding hBNP using a porcine cDNA probe, the present Inventors also failed to obtain human BNP cDNA using a 10-20 bp pBNP probe. The failure of others to produce the claimed invention, and the arrival at a solution to unexpected and unforeseen problems have long been considered objective indicia of the non-obviousness of an invention. See Graham v. John Deere, 383 U.S. 1, 148 U.S.P.Q. 459 (1966); Eibel Process Co. v. Minnesota & Ontario Paper Co., 261 U.S. 45, 43 S.Ct. 322 (1923); and Reeves Instrument Corp. v. Beckman Instruments, Inc., 444 F.2d 263, 170 U.S.P.Q. 74 (9th Cir. 1971), cert. denied, 404 U.S. 751 (1971).

Furthermore, the low homology (70.0%) between human prepro-BNP and porcine prepro-BNP (results determined by the present Inventors, disclosed by Sudoh et al [*Biochem. Biophys. Res. Comm.*, 159:1427-1434]) presents a sharp contrast to the more highly conserved mammalian ANP's, thus introducing a further unexpected problem in cloning hBNP. This unexpected problem makes it surprising that the method of Group XXIX, Claim 34 (concerning production of hBNP cDNA), could be obtained, given the level of ordinary skill and the knowledge in this field at the time of filing grandparent U.S. application Serial No. 07/486,827 (March 1, 1990) (see paragraph 9, page 4 of the Declaration of Sudoh).

Therefore, one of ordinary skill would not have had a reasonable expectation of success for the method of Group

XXIX, Claim 34, from the knowledge present in the art at the time grandparent application Serial No. 07/486,827 was filed.

Finally, as discussed above, Seilhamer et al disclose their complete failure to hybridize cDNA encoding porcine BNP to human DNA, even though there was every reason to believe that it would succeed (see col. 8, lines 40-54 and col. 9, lines 32-35 and 45-47 of Seilhamer et al). In fact, Seilhamer et al specifically state:

"There was every reason to believe that porcine BNP should be capable of hybridizing to human NRP under appropriate conditions; however no conditions could be determined under which pBNP would hybridize to a human library. This was surprising in that, in an evolutionary sense, porcine BNP is more likely to be related to the corresponding human protein, than is a corresponding canine protein. It was thus unexpected that porcine BNP was unable to identify human NRP...." (col. 8, lines 44-54; emphasis added).

Consequently, the conclusion in the Official Action of February 6, 1995, that it is not surprising that Seilhamer et al failed to isolate the human BNP genomic clone using pBNP cDNA is not accurate since Seilhamer et al themselves state that is surprising. As a result, the success of the present Inventors in obtaining DNA encoding human BNP is surprising and unexpected, particularly in view of the failure of Seilhamer et al to hybridize DNA encoding pBNP to human DNA. Thus, the method of Group XXIX, Claim 34, is not obvious in view of the cited references, based on the evidence of record.

Consequently, Group XXIX, Claim 34, is fully and independently patentable over the cited references. Therefore, this ground of rejection is clearly in error, and should be withdrawn.

GROUP XXX -- CLAIM 34

Group XXX, Claim 35, depends from Group XXIX, Claim 34. Therefore, Group XXX, Claim 35, includes all of the limitations of Group XXIX, Claim 34, and all arguments presented above in support of Group XXIX, Claim 34, are incorporated hereinbelow in support of Group XXX, Claim 35.

Group XXX, Claim 35, includes the further limitation that the probe consists essentially of the following base sequence:

CGG GCA CCA CGA AGC CCC AAG ATG GTG CAA

GGG TCT GGC TGC TTT GGG AGG AAG ATG GAC CGG ATC AGC

TCC TCC AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT,

a sequence commonly recited in both Groups XVI and XXX, Claims 29 and 35. Therefore, all arguments presented above in support of Group XVI, Claim 29, are incorporated hereinbelow in support of Group XXX, Claim 35.

As discussed above in support of Group XVI, Claim 29, at least 22 structural differences exist between the sequence recited in Group XXX, Claim 35, and the structurally closest sequence disclosed by the cited references (Maekawa et al,

Fig. 3, from position 286 to position 393). One of ordinary skill would not necessarily expect a probe as structurally different from the closest sequence disclosed by the cited references as is the sequence recited in Group XXX, Claim 35, to be successful in the method of Group XXX, Claim 35. Thus, the method of Group XXX, Claim 35, is not obvious from the cited references in view of the structural differences between the sequence recited therein and closest possible polynucleotide suggested by the cited references.

Furthermore, as discussed above in support of Group XXIX, Claim 34, one of ordinary skill would not have had a reasonable expectation of success in arriving at the present invention from the teachings of the cited references (see the Declaration of Sudoh dated October 12, 1994 and filed October 20, 1994). Thus, the evidence of record supports the patentability of the present method.

For example, neither (1) the 70% degree of homology between human atrial natriuretic peptide (hANP) and porcine BNP (pBNP) taught by Sudoh et al (R) and (T) nor (2) the 50.6-65.7% degree of homology between hANP mRNA and pBNP mRNA taught by Maekawa et al is sufficiently high for one of ordinary skill to reasonably expect success in cloning and isolating cDNA encoding human BNP based on the sequence of DNA encoding porcine BNP (see paragraph 5, page 3 of the Declaration of Sudoh dated October 12, 1994 and filed October 20, 1994).

Further, assuming that one of ordinary skill expects the same degree of homology between hBNP and other mammalian BNPs as is observed between hANP and other mammalian ANPs, Sudoh et al (R) and (T), Maekawa et al and Oikawa et al appear to indicate that one might expect a probe based on the pBNP gene to lead to cloning of a hANP gene, rather than a hBNP gene (see paragraph 6, pages 3-4 of the Declaration).

In addition to the failure of Seilhamer et al to isolate a polynucleic acid encoding hBNP using a porcine cDNA probe, the present Inventors also failed to obtain human BNP cDNA using a 10-20 bp pBNP probe. The failure of others to produce the claimed invention, and the arrival at a solution to unexpected and unforeseen problems have long been considered objective indicia of the non-obviousness of an invention. See Graham v. John Deere, 383 U.S. 1, 148 U.S.P.Q. 459 (1966); Eibel Process Co. v. Minnesota & Ontario Paper Co., 261 U.S. 45, 43 S.Ct. 322 (1923); and Reeves Instrument Corp. v. Beckman Instruments, Inc., 444 F.2d 263, 170 U.S.P.Q. 74 (9th Cir. 1971), cert. denied, 404 U.S. 751 (1971).

Furthermore, the low homology (70.0%) between human prepro-BNP and porcine prepro-BNP (results determined by the present Inventors, disclosed by Sudoh et al [*Biochem. Biophys. Res. Comm.*, 159:1427-1434]) presents a sharp contrast to the more highly conserved mammalian ANP's, thus introducing a further unexpected problem in cloning hBNP. This unexpected problem makes it surprising that the method of Group XXX,

Claim 35 (concerning production of hBNP cDNA), could be obtained, given the level of ordinary skill and the knowledge in this field at the time of filing grandparent U.S. application Serial No. 07/486,827 (March 1, 1990) (see paragraph 9, page 4 of the Declaration of Sudoh).

Therefore, one of ordinary skill would not have had a reasonable expectation of success for the method of Group XXX, Claim 35, from the knowledge present in the art at the time grandparent application Serial No. 07/486,827 was filed.

Finally, as discussed above, Seilhamer et al disclose their complete failure to hybridize cDNA encoding porcine BNP to human DNA, even though there was every reason to believe that it would succeed (see col. 8, lines 40-54 and col. 9, lines 32-35 and 45-47 of Seilhamer et al). In fact, Seilhamer et al specifically state:

"There was every reason to believe that porcine BNP should be capable of hybridizing to human NRP under appropriate conditions; however no conditions could be determined under which pBNP would hybridize to a human library. This was surprising in that, in an evolutionary sense, porcine BNP is more likely to be related to the corresponding human protein, than is a corresponding canine protein. It was thus unexpected that porcine BNP was unable to identify human NRP...." (col. 8, lines 44-54; emphasis added).

Consequently, the conclusion in the Official Action of February 6, 1995, that it is not surprising that Seilhamer et al failed to isolate the human BNP genomic clone using pBNP cDNA is not accurate since Seilhamer et al themselves state

that is surprising. As a result, the success of the present Inventors in obtaining DNA encoding human BNP is surprising and unexpected, particularly in view of the failure of Seilhamer et al to hybridize DNA encoding pBNP to human DNA. Thus, the method of Group XXX, Claim 35, is not obvious in view of the cited references, based on the evidence of record.

Consequently, Group XXX, Claim 35, is fully and independently patentable over the cited references. Therefore, this ground of rejection is clearly in error, and should be withdrawn.

(v) (ii)(iii): There are no other grounds of rejection in this application.

CONCLUSION

Accordingly, each of Claims in the present application is fully patentable over the cited references. Therefore, this ground of rejection is in error, and should be withdrawn.

Consequently, the Final Rejection of Claims 2-7 and 10-35 in this application as set forth in the Official Action dated February 6, 1995, is improper, and should be REVERSED.

Respectfully submitted,

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APPENDIX

14. A cDNA consisting essentially of a base sequence encoding a polypeptide having the following amino acid sequence:

H-Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser
Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His-OH.

15. The cDNA of Claim 14, further consisting essentially of a base sequence encoding the amino acid sequence H-Gly-Ser-Gly covalently bound to the H-Cys amino acid through a peptide bond.

16. The cDNA of Claim 14, further consisting essentially of a base sequence encoding the amino acid sequence H-Ser-Pro-Lys-Met-Val-Gln-Gly-Ser-Gly covalently bound to the H-Cys amino acid through a peptide bond.

17. The cDNA of Claim 16, further consisting essentially of a base sequence encoding the N-terminal amino acid sequence:

His Pro Leu Gly Ser Pro Gly Ser Ala Ser Asp Leu Glu Thr Ser
Gly Leu Gln Glu Gln Arg Asn His Leu Gln Gly Lys Leu Ser Glu
Leu Gln Val Glu Gln Thr Ser Leu Glu Pro Leu Gln Glu Ser Pro
Arg Pro Thr Gly Val Trp Lys Ser Arg Glu Val Ala Thr Glu Gly
Ile Arg Gly His Arg Lys.

18. The cDNA of Claim 17, further consisting essentially of a base sequence encoding the N-terminal amino acid sequence:

Met Asp Pro Gln Thr Ala Pro Ser Arg Ala Leu Leu Leu Leu
Leu Phe Leu His Leu Ala Phe Leu Gly Gly Arg Ser.

19. The cDNA of Claim 14, having the following base sequence:

TGC TTT GGG AGG AAG ATG GAC CGG ATC AGC TCC TCC
AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT.

20. The cDNA of Claim 15, having the following base sequence:

GGG TCT GGC TGC TTT GGG AGG AAG ATG GAC CGG ATC AGC
TCC TCC AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT.

21. The cDNA of Claim 16, having the following base sequence:

AGC CCC AAG ATG GTG CAA GGG TCT GGC TGC TTT
GGG AGG AAG ATG GAC CGG ATC AGC TCC TCC AGT
GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT.

22. The cDNA of Claim 17, having the following base sequence:

CAC CCG CTG GGC AGC CCC GGT TCA GCC TCG GAC TTG GAA ACG TCC
GGG TTA CAG GAG CAG CGC AAC CAT TTG CAG GGC AAA CTG TCG GAG
CTG CAG GTG GAG CAG ACA TCC CTG GAG CCC CTC CAG GAG AGC CCC

CGT CCC ACA GGT GTC TGG AAG TCC CGG GAG GTA GCC ACC GAG GGC
ATC CGT GGG CAC CGC AAA ATG CTC CTC TAC ACC CTG CGG GCA CCA
CGA AGC CCC AAG ATG GTG CAA GGG TCT GGC TGC TTT GGG AGG AAG
ATG GAC CGG ATC AGC TCC TCC AGT GGC CTG GGC TGC AAA GTG CTG
AGG CGG CAT.

23. The cDNA of Claim 18, having the following base sequence:

ATG GAT CCC CAG ACA GCA CCT TCC CGG GCG CTC CTG CTC CTG CTC
TTC TTG CAT CTG GCT TTC CTG GGA GGT CGT TCC CAC CCG CTG GGC
AGC CCC GGT TCA GCC TCG GAC TTG GAA ACG TCC GGG TTA CAG GAG
CAG CGC AAC CAT TTG CAG GGC AAA CTG TCG GAG CTG CAG GTG GAG
CAG ACA TCC CTG GAG CCC CTC CAG GAG AGC CCC CGT CCC ACA GGT
GTC TGG AAG TCC CGG GAG GTA GCC ACC GAG GGC ATC CGT GGG CAC
CGC AAA ATG GTC CTC TAC ACC CTG CGG GCA CCA CGA AGC CCC AAG
ATG GTG CAA GGG TCT GGC TGC TTT GGG AGG AAG ATG GAC CGG ATC
AGC TCC TCC AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT.

24. The cDNA of Claim 14, obtained by screening a human cDNA library.

25. The cDNA of Claim 24, wherein said screening comprises hybridizing a probe having a DNA sequence encoding a part of porcine brain natriuretic peptide.

26. The cDNA of Claim 25, wherein said probe is obtained by digesting a complete or incomplete cDNA clone encoding

porcine brain natriuretic peptide with endonucleases XhoI and RsaI.

27. The cDNA of Claim 26, wherein said probe encodes the amino acid sequence:

H-Gly Ser Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser
Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His-OH.

28. The cDNA of Claim 26, wherein said probe is labelled.

29. The cDNA of Claim 27, wherein said probe consists essentially of the following base sequence:

CGG GCA CCA CGA AGC CCC AAG ATG GTG CAA
GGG TCT GGC TGC TTT GGG AGG AAG ATG GAC CGG ATC AGC
TCC TCC AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT.

10. A recombinant DNA sequence comprising a base sequence encoding a polypeptide having the following amino acid sequence:

H-Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser
Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His-OH.

11. The recombinant DNA of Claim 10, wherein said polypeptide further comprises the amino acid sequence H-Gly-Ser-Gly covalently bound to the H-Cys amino acid through a peptide bond.

12. The recombinant DNA sequence of Claim 10, having the following base sequence:

TGC TTT GGG AGG AAG ATG GAC CGG ATC AGC TCC TCC
AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT.

13. The recombinant DNA sequence according to Claim 11, having the following base sequence:

GGG TCT GGC TGC TTT GGG AGG AAG ATC GAC CGG ATC AGC
TCC TCC AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT.

2. A recombinant DNA sequence comprising a base sequence encoding a polypeptide possessing natriuretic activity, wherein said polypeptide has the following amino acid sequence:

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys
Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val
Leu Arg Arg His.

3. A recombinant DNA sequence comprising a base sequence encoding a polypeptide possessing natriuretic activity, wherein said polypeptide has the following amino acid sequence:

His Pro Leu Gly Ser Pro Gly Ser Ala Ser Asp Leu Glu
Thr Ser Gly Leu Gln Glu Gln Arg Asn His Leu Gln Gly
Lys Leu Ser Glu Leu Gln Val Glu Gln Thr Ser Leu Glu
Pro Leu Gln Glu Ser Pro Arg Pro Thr Gly Val Trp Lys
Ser Arg Glu Val Ala Thr Glu Gly Ile Arg Gly His Arg

Lys Met Val Leu Tyr Thr Leu Arg Ala Pro Arg Ser Pro
Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met
Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val
Leu Arg Arg His.

4. A recombinant DNA sequence comprising a base sequence encoding a polypeptide possessing natriuretic activity, wherein said polypeptide has the following amino acid sequence:

Met Asp Pro Gln Thr Ala Pro Ser Arg Ala Leu Leu Leu Leu
Phe Leu His Leu Ala Phe Leu Gly Gly Arg Ser His Pro Leu
Gly Ser Pro Gly Ser Ala Ser Asp Leu Glu Thr Ser Gly Leu
Gln Glu Gln Arg Asn His Leu Gln Gly Lys Leu Ser Glu Leu
Gln Val Glu Gln Thr Ser Leu Glu Pro Leu Gln Glu Ser Pro
Arg Pro Thr Gly Val Trp Lys Ser Arg Glu Val Ala Thr Glu
Gly Ile Arg Gly His Arg Lys Met Val Leu Tyr Thr Leu Arg
Ala Pro Arg Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly
Cys Lys Val Leu Arg Arg His.

5. The recombinant DNA sequence according to Claim 2 having the following base sequence:

AGC CCC AAG ATG GTG CAA GGG TCT GGC TGC TTT
GGG AGG AAG ATG GAC CGG ATC AGC TCC TCC AGT
GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT.

6. The recombinant DNA sequence according to Claim 3 having the following base sequence:

CAC CCG CTG GGC AGC CCC GGT TCA GCC TCG GAC TTG GAA ACG
TCC GGG TTA CAG GAG CAG CGC AAC CAT TTG CAG GGC AAA CTG
TCG GAG CTG CAG GTG GAG CAG ACA TCC CTG GAG CCC CTC CAG
GAG AGC CCC CGT CCC ACA GGT GTC TGG AAG TCC CGG GAG GTA
GCC ACC GAG GGC ATC CGT GGG CAC CGC AAA ATG CTC CTC TAC
ACC CTG CGG GCA CCA CGA AGC CCC AAG ATG GTG CAA GGG TCT
GGC TGC TTT GGG AGG AAG ATG GAC CGG ATC AGC TCC TCC AGT
GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT

7. The recombinant DNA sequence according to Claim 4 having the following base sequence:

ATG GAT CCC CAG ACA GCA CCT TCC CGG GCG CTC CTG CTC CTG
CTC TTC TTG CAT CTG GCT TTC CTG GGA GGT CGT TCC CAC CCG
CTG GGC AGC CCC GGT TCA GCC TCG GAC TTG GAA ACG TCC GGG
TTA CAG GAG CAG CGC AAC CAT TTG CAG GGC AAA CTG TCG GAG
CTG CAG GTG GAG CAG ACA TCC CTG GAG CCC CTC CAG GAG AGC
CCC CGT CCC ACA GGT GTC TGG AAG TCC CGG GAG GTA GCC ACC
GAG GGC ATC CGT GGG CAC CGC AAA ATG GTC CTC TAC ACC CTG
CGG GCA CCA CGA AGC CCC AAG ATG GTG CAA GGG TCT GGC TGC
TTT GGG AGG AAG ATG GAC CGG ATC AGC TCC TCC AGT GGC CTG
GGC TGC AAA GTG CTG AGG CGG CAT

30. A method of producing cDNA, comprising:
hybridizing a probe having a DNA sequence encoding a part
of porcine brain natriuretic peptide to a human cDNA library;

selecting a positive clone; and
isolating said cDNA of said positive clone.

31. The method of Claim 30, wherein said cDNA encodes human brain natriuretic peptide.

32. The method of Claim 31, wherein said probe is labelled.

33. The method of Claim 31, wherein said probe is obtained by digesting a complete or incomplete cDNA clone encoding porcine brain natriuretic peptide with endonucleases XhoI and RsaI.

34. The method of Claim 33, wherein said probe encodes the amino acid sequence:

H-Gly Ser Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser
Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His-OH.

35. The method of Claim 34, wherein said probe consists essentially of the following base sequence:

CGG GCA CCA CGA AGC CCC AAG ATG GTG CAA
GGG TCT GGC TGC TTT GGG AGG AAG ATG GAC CGG ATC AGC
TCC TCC AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT.